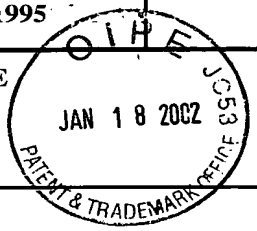
9200/1609

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): **Batchelor et al.**			Docket No. **G1070US2**
Serial No. **08/405,120**	Filing Date **March 16, 1995**	Examiner	Group Art Unit

Invention: **ADROSTENONE DERIVATIVE**



MAIL DATE CANCELLED

I hereby certify that this **Application for Extension of Patent Term, Exhibits 1-9, & Declaration**
(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Commissioner of Patents and Trademarks, Washington, D.C. 20231-0001 on 1/18/02
(Date)

Allyson K. Jacobs
(Typed or Printed Name of Person Mailing Correspondence)

Allyson K. Jacobs
(Signature of Person Mailing Correspondence)

EL395889738US
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TRANSMITTALLETTER (General - Patent Issued)	Docket No. G1070US2

Patentee(s): **Kenneth W. Batchelor and Stephen V. Frye**

U.S. Patent No.	Issue Date
5,565,467	**October 15, 1996**

Title: **ANDROSTENONEDERIVATIVE**

TO THE COMMISSIONEROF PATENTS AND TRADEMARKS:

Transmitted herewith is:

Declaration of David J. Levy, Ph.D. Under 37 C.F.R. 1.740(b)
Application for Extension of Patent Term under 35 U.S.C. 156
Exhibits 1 through 9

- ☐ No additional fee is required.
- ☐ A check in the amount of is attached.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **07-1392** as described below. A duplicate copy of this sheet is enclosed.
  - ☒ Charge the amount of **$1,120.00**
  - ☒ Credit any overpayment.
  - ☒ Charge any additional fee required.

Signature

Dated: Jan. 18, 2002

Amy H. Fix, Reg. No. 42,616
Attorney for Applicants
GlaxoSmithKline
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709-3398
Telephone: (919) 483-8911
Facsimile: (919) 483-7988

23347
PATENT TRADEMARK OFFICE

cc:

I certify that this documentand fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissionerof Patents and Trademarks, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

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Express Mail Label No.:
EL395889738US

TRANSMITTAL LETTER (General - Patent Issued)	Docket No. G1070US2

Patentee(s): **Kenneth W. Batchelor and Stephen V. Frye**

U.S. Patent No.	Issue Date
5,565,467	October 15, 1996

Title: **ANDROSTENONE DERIVATIVE**

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

Transmitted herewith is:

Declaration of David J. Levy, Ph.D. Under 37 C.F.R. 1.740(b)
Application for Extension of Patent Term under 35 U.S.C. 156
Exhibits 1 through 9

- ☐ No additional fee is required.
- ☐ A check in the amount of _____ is attached.
- ☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **07-1392** as described below. A duplicate copy of this sheet is enclosed.
  - ☒ Charge the amount of **$1,120.00**
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Signature

Dated: Jan. 18, 2002

Amy H. Fix, Reg. No. 42,616
Attorney for Applicants
GlaxoSmithKline
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709-3398
Telephone: (919) 483-8911
Facsimile: (919) 483-7988

23347
PATENT TRADEMARK OFFICE

CC:

I certify that this document and fee is being deposited on _____ with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

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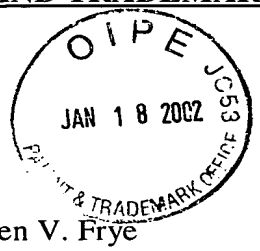
G1070US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In Re: US Patent No. 5,565,467

Issued: October 15, 1996

Inventors: Kenneth W. Batchelor and Stephen V. Frye

Assignee: SmithKline Beecham Corporation (formerly Glaxo Wellcome Inc.)

For: ANDROSTENONE DERIVATIVE

Re: Patent Term Extension for U.S. Patent No. 5,565,467

Commissioner of Patents
Box Patent Extension
Washington DC 20231

Sir:

Transmitted herewith is an Application for Extension of a Patent Term under 35 U.S.C. 156 with regard to U.S. Patent No. 5,565,467.

The Commissioner of Patent and Trademarks is hereby authorized to charge deposit account number 07-1392 in the amount of $1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392. Triplicate copies of this letter are enclosed.

Express Mail Label No.:
EL395889738US

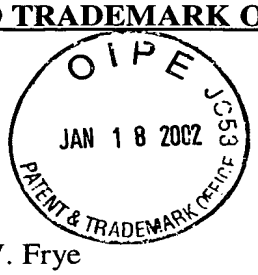
Inquiries and correspondences relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Patent Counsel
GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723

Respectfully submitted,

By: _____ 11/18/02
David J. Levy, Ph. D.
Reg. No. 27,655
Attorney for Applicant
SmithKlineBeecham Corporation

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In Re: US Patent No. 5,565,467

Issued: October 15, 1996

Inventors: Kenneth W. Batchelor and Stephen V. Frye

Assignee: SmithKline Beecham Corporation (formerly Glaxo Wellcome Inc.)

For: ANDROSTENONE DERIVATIVE

Re: Patent Term Extension for U.S. Patent No. 5,565,467

Commissioner of Patents
Box Patent Extension
Washington, DC 20231

DECLARATION OF DAVID J. LEVY, PH.D. UNDER 37 C.F.R. 1.740(B)

Sir:

I, David J. Levy, residing in Wake Forest, North Carolina, declare as follows:

(1) I am a patent attorney authorized to practice before the United States Patent and Trademark Office; my registration number is 27,655.

(2) I make this declaration as Patent Counsel for SmithKline Beecham Corporation, a corporation of the State of Pennsylvania, having a place of business at Five Moore Drive, Research Triangle Park, North Carolina, 27709, having general authority to act on its behalf in patent matters.

(3) Pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1), SmithKline Beecham Corporation is the record owner and assignee of the entire right title and interest in and to US Patent No. 5,565,467 issued October 15, 1996 for ANDROSTENONE DERIVATIVE by virtue of assignment to Glaxo, Inc., recorded in the United States Patent and Trademark Office on March 16, 1995, Reel 7406, Frame 0967; and corporate name change of Glaxo, Inc. to Glaxo Wellcome, Inc.; and subsequent corporate merger between Glaxo Wellcome, Inc. and SmithKline Beecham Corporation, see EXHIBITS 1 and 2 to the above-referenced application.

(4) I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in SmithKline Beecham Corporation by virtue of the assignment, corporate name change, and corporate merger noted in paragraph (3).

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(5) I have reviewed and understand the contents of the Application submitted herewith on behalf of SmithKline Beecham Corporation, requesting a 769-day extension of the term of US Patent No. 5,565,467.

(6) I believe that US Patent No 5,565,467 is subject to extension pursuant to 37 C.F.R. §1.710.

(7) I believe that a 769-day extension of the term of US Patent No. 5,565,467 is justified under 35 U.S.C. §156 and applicable regulations.

(8) I believe that US Patent No. 5,565,467, for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

(9) Any inquiries and correspondence relating to this Application for Patent Term Extension of US Patent No. 5,565,467 are to be directed to:

David J. Levy, Ph.D.
Intellectual Property Counsel
GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723
fax: (919) 483-7988

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,565,467 and any extensions thereof.

David S. Levy

January 18, 2002

David J. Levy, Ph. D.
Reg. No. 27,655
Attorney for Applicant
SmithKlineBeecham Corporation

Date

23347

PATENT TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: US Patent No. 5,565,467

Issued: October 15, 1996

Inventors: Kenneth W. Batchelor and Stephen V. Frye

Assignee: SmithKlineBeecham Corporation (formerly Glaxo Wellcome, Inc.)

For: ANDROSTENONE DERIVATIVE

Re: Patent Term Extension for U.S. Patent No. 5,565,467

Commissioner of Patents
Box Patent Extension
Washington DC 20231

Sir:

Applicant, SmithKlineBeecham Corporation, a corporation of the State of Pennsylvania, represents, pursuant to 35 U.S.C. 156(d)(1), that SmithKlineBeecham Corporation, is the record owner and assignee of the entire right title and interest in and to: Letters Patent of the United States of America No. 5,565,467; granted on October 15, 1996 for ANDROSTENONE DERIVATIVE by virtue of an assignment to Glaxo, Inc. dated March 16, 1995, which assignment was recorded in the United States Patent and Trademark Office on March 16, 1995 on Reel 7406, Frame 0967, followed by a Corporate Name Change to Glaxo Wellcome, Inc., followed by a Corporate Merger between Glaxo Wellcome Inc. and SmithKlineBeecham Corporation. A copy of the above-referenced assignment is attached at EXHIBIT 1. A copy of the Corporate Name Change is attached hereto at EXHIBIT 2A. A copy of the Articles of Merger regarding the corporate entity is attached at EXHIBIT 2B.

Applicants further represent, pursuant to 37 C.F.R. 1.785(d), that Applicant is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for dutasteride soft gelatin capsules (hereinafter, "DUTASTERIDE"). A copy of the Food and Drug Administration (FDA) Approval Letter for DUTASTERIDE is attached hereto as EXHIBIT 3.

Applicant hereby submits this Application for Extension of Patent Term under 35 U.S.C. 156 by providing the following information pursuant to 37 C.F.R. 1.740. For convenience, the information contained in this application will be presented according to the format set forth in 37 C.F.R. 1.740(a).

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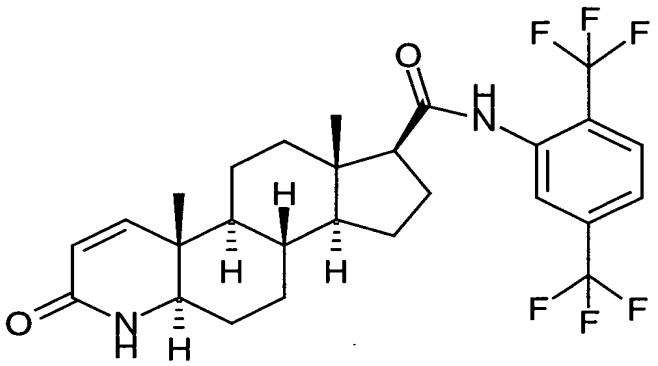
(1) This application for patent term extension is based upon the regulatory review period before the FDA, of Applicant's approved product, DUTASTERIDE soft gelatin capsules. The only active ingredient in DUTASTERIDE soft gelatin capsules is dutasteride. A copy of the package insert approved by the FDA as part of New Drug Application 21-319 (NDA) is attached hereto as EXHIBIT 4. Identification of the approved product is provided as follows:

Chemical Name(s): (5α, 17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-aza- androst-1-ene-17-carboxamide

Molecular formula: $C_{27}H_{30}F_6N_2O_2$

Structural formula:



Molecular weight: 528.5

Physical Form: white to pale yellow powder

(2) The approved product, DUTASTERIDE soft gelatin capsules was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, section 505 (21 U.S.C. 355). See EXHIBIT 3.

(3) DUTASTERIDE soft gelatin capsules received permission for commercial marketing and use under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on November 20, 2001. See EXHIBIT 3.

(4) Dutsteride, the only active ingredient in DUTASTERIDE soft gelatin capsules has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60-day period, which will expire on January 19, 2002.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

U.S. Pat. No.: 5,565,467

Inventors: Kenneth W. Batchelor and Stephen V. Frye

Assignee: SmithKline Beecham Corporation

For: ANDROSTENONE DERIVATIVE

Issued: October 15, 1996

Expiration Date: October 15, 2013

(7) A complete copy of the patent identified in paragraph (6) above is attached hereto as EXHIBIT 5.

(8) Regarding U.S. Pat. No. 5,565,467:

(a) A petition for correction of inventorship has been filed for this patent.

The patentees, through error without deceptive intent, incorrectly included George F. Dorsey, Jr. and Robert A. Mook, Jr. as inventors. The patentees filed a Petition to Correct Inventorship under 35 U.S.C. §256 and 37 C.F.R. §1.324 and await the Certificate of Correction from the United States Patent and Trademark Office. See EXHIBIT 6.

(b) A maintenance fee payment statement made with respect to U.S. Patent 5,565,467 is attached hereto as EXHIBIT 7.

(c) No reexamination certificate exists in respect of U.S. Patent 5,565,467.

(9) United States Patent 5,565,467 claims the active ingredient, dutasteride, in the approved product, soft gelatin capsules. Applicant hereinbelow lists each applicable patent claim and demonstrates the manner in which each applicable claim reads on the approved product or method of using the approved product.

(a) Claim 1 reads as follows: "17β-N-(2,5-bis(Trifluoromethyl) phenylcarbomoyl-4-aza-5α-androst-1-en-3-one or a pharmaceutically acceptable solvate thereof."

Claim 1 reads on the approved product, DUTASTERIDE soft gelatin capsules, because the active ingredient of the approved product, dutasteride, is 17β-N-(2,5-bis(Trifluoromethyl) phenylcarbomoyl-4-aza-5α-androst-1-en-3-one.

(b) Claim 2 reads as follows: "A pharmaceutical formulation comprising the compound of claim 1 and a pharmaceutically acceptable carrier thereof."

Claim 2 reads on the approved product, DUTASTERIDE soft gelatin capsules, because the approved product is a pharmaceutical composition which contains the active ingredient dutasteride, which is a compound according to claim 1 (*see* item 9(a) *supra*), together with a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene, which are pharmaceutically acceptable carriers.

(c) Claim 3 reads as follows: "A pharmaceutical formulation comprising a safe and effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier thereof."

Claim 3 reads on the approved product, DUTASTERIDE soft gelatin capsules, because the approved product is a pharmaceutical composition which contains a safe and effective amount of the active ingredient dutasteride, which is a compound according to claim 1 (*see* item 9(a) *supra*), together with a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene, which are pharmaceutically acceptable carriers.

(10) The relevant dates and information pursuant to 35 U.S.C 156(g) necessary to enable the Secretary of Health and Human Resources to determine the applicable regulatory review period are as follows:

(a) Effective Dates and Numbers of the INDs
The first Investigational New Drug Application ("IND") for alosetron hydrochloride became effective 24 April 1995; it was designated IND No. 47,838 (GI198745 (5-alpha reductase inhibitor)). See EXHIBIT 8A.

(b) Issue Date of Patent
US Patent No. 5,565,467 issued 15 October 1996 and claims a new drug and drug product. See EXHIBIT 5.

(c) Submission Date and Number of NDA
The NDA for DUTASTERIDE soft gelatin capsules was submitted on 21 December 2000 and was designated NDA No. 21-319. See EXHIBIT 8B.

(d) Approval Date of NDA
NDA No. 21-107 for DUTASTERIDE soft gelatin capsules was approved by the FDA on 20 November 2001. See EXHIBIT 3.

(11) A brief description of the significant activities undertaken by Applicant during both the IND and NDA regulatory periods is presented in a chronological form and is attached hereto as EXHIBIT 8 (including EXHIBITS 8A and 8B), "Due Diligence Log".

(a) The Due Diligence Log reflects significant communications with FDA during regulatory periods. Such communications include, but are not limited to: submission of preclinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.

(b) Periods between such communications enumerated in the Due Diligence Log reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

(12) Applicant is of the opinion that U.S. Patent 5,565,467 is eligible for a 769-day extension, up through and including November 20, 2015, taking into account the 14-year limitation under 35 U.S.C. 156(c)(3). See EXHIBIT 9.

(a) Applicant has satisfied the eligibility criteria necessary to obtain a patent term extension pursuant to 35 U.S.C. 156.

(1) 35 U.S.C. 156(a)
U.S. Patent No. 5,565,467 claims a drug product.

(2) 35 U.S.C. 156(a)(1)
The term of U.S. Patent No. 5,565,467 has not expired before the submission of application.

(3) 35 U.S.C. 156(a)(2)
The term of U.S. Patent No. 5,565,467 has never been extended.

(4) 35 U.S.C. 156(a)(3)
The application for extension is submitted by the agent of the owner of record in accordance with the requirements of 35 U.S.C. 156(d) and 37 C.F.R. 1.710 *et seq.*

(5) 35 U.S.C. 156(a)(4)
The approved product, DUTASTERIDE soft gelatin capsules, has been subject to a regulatory review period before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)
The commercial marketing or use of the approved product, DUTASTERIDE soft gelatin capsules, after the regulatory review period is the first permitted commercial marketing or use of the approved product under the provisions under which such regulatory review period occurred.

(b) Applicant herewith claims a patent term extension of 769 days, taking into account the 14-year limitation under 35 U.S.C. 156(c)(3), for U.S. Patent No. 5,565,467 pursuant to U.S.C. 156(g) as follows:

(1) One half the IND regulatory review period for the approved product beginning 16 Oct 1996 (the IND period occurring after the date of issuance of U.S. Patent No. 5,565,467) and ending on 20 December 2000 (one day prior to the date on which the NDA for the approved product was initially submitted).

(2) The full term of the NDA regulatory review period commencing 21 December 2000 (the date NDA 21-319 for the approved product was originally submitted) and ending on 20 November 2001 (the date on which NDA 21-319 was approved).

(3) Reducing the sum of Items 12(b)(1) and 12(b)(2) *supra* based upon the 14 year limitation under 35 U.S.C. §156(c)(3).

(4) The total extension applicable for U.S. Patent No. 5,565,467 is equal 769 days. See EXHIBIT 9.

(c) Applicant herewith claims an extension expiry date of **20 November 2015** for U.S. Patent 5,565,467.

(1) The expiration of U.S. Patent 5,565,467 is 15 October 2013.

(2) 35 U.S.C. 156(c)(3) requires that term extensions if necessary be reduced in order to limit the expiration date of a patent receiving term extension to 14 years from the date of NDA approval. The expiration date of U.S. Patent 5,565,467 is therefore limited by the provisions of 35 U.S.C. 156(c)(3). See EXHIBIT 9.

(3) Extending the 15 October 2013 date by 769 days would result in an expiration date of **20 November 2015**. See EXHIBIT 9.

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

(14) The Commissioner of Patents is hereby authorized to charge deposit account number 07-1392 in the amount of $1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392.

(15) Inquiries and correspondences relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Patent Counsel
GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-2723

b) Applicants submit three original copies of the application papers.

c) Submitted herewith is a Declaration by David J. Levy, Ph.D., Patent Counsel for Glaxo Wellcome Inc., which meets the criteria set forth in 37 CFR 1.740(b), and includes a Rule 3.73(b) certification on behalf of SmithKline Beecham Corporation, which establishes the right of SmithKline Beecham Corporation, as assignee, to take action in the Patent and Trademark Office in connection with this patent, including the naming of Applicant as its agent for purposes of filing this application, and grants power of attorney to the named registered patent attorneys.

The undersigned hereby certifies that this Application for Extension of Patent Term Under 35 U.S.C. 156, including Exhibits 1-9 and supporting papers, is being submitted as triplicate originals.

Respectfully submitted,

By: _____ 1/18/02

David J. Levy, Ph. D.
Reg. No. 27,655
Attorney for Applicant
SmithKlineBeecham Corporation

EXHIBIT 1

Assignment to Glaxo Inc. of Application for Letters Patent

of United States Patent Application No. 08/405,120

U.S. Patent No. 5,565,467

Express Mail Label No.:
EL395889738US

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE: 05/09/95
TO:

CHARLES E. DADSWELL
GLAXO INC.
LEGAL-PATENT GROUP
FIVE MOORE DRIVE
RTP, NC 27709

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR:
FRYE, STEPHEN V. DOC DATE: 03/16/95

ASSIGNOR:
MOOK, ROBERT A., JR. DOC DATE: 03/16/95

ASSIGNOR:
DORSEY, GEORGE F., JR. DOC DATE: 03/16/95

ASSIGNOR:
BATCHELOR, KENNETH W. DOC DATE: 03/16/95

RECORDATION DATE: 03/16/95 NUMBER OF PAGES 005 REEL/FRAME 7406/0967

DIGEST: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNEE:
GLAXO INC.
LEGAL-PATENT GROUP
5 MOORE DRIVE
RTP, NC 27709

SERIAL NUMBER 8-405120 FILING DATE 03/16/95
PATENT NUMBER ISSUE DATE 00/00/00

Dorothy E. Fuller

EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

08/405120

U. PARTMENT OF COMMERCE
Patent and Trademark Office

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Stephen V. Frye, Robert A. Mook, Jr., George F. Dorsey, Jr., Kenneth W. Batchelor

Additional name(s) of conveying party(ies) attached? No

3. Nature of conveyance: IS

X Assignments Merger

Security Agreement Change of Name

Other _____

Execution Date: March 16, 1995

2. Name and address of receiving party(ies):

Name: GLAXO INC.

Internal Address: Legal-Patent Group

Street Address: 5 MOORE DRIVE

City: RTP State: NC Zip: 27709

Additional name(s) & address(es) attached? Yes No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: March 16, 1995

A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? Yes X No

RECEIVED
95 APR 18 AM 9:00
ASSIGNMENT BRANCH

REEL 7406 FRAME 917

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Charles E. Dadswell

Internal Address: Glaxo Inc.
Legal-Patent Group

Street Address: Five Moore Drive

City: RTP State: NC Zip: 27709

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41):.....$ 40.00

Enclosed

X Authorized to be charged to deposit account.

Previously Submitted

8. Deposit account number: 07-1392

(Attach copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

SC13130 04/03/95 08405120 07-1392 130 581 40.00CH

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Charles E. Dadswell — 03/16/95

Name of Person Signing — Signature — Date

Total number of pages comprising cover sheet: 1

93770321

G1070-2

ASSIGNMENT

I, Kenneth W. Batchelor, for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, Kenneth W. Batchelor, hereunto set my hand and seal this 16 day of March, 1995.

KWBatchelor
Kenneth W. Batchelor

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, Kenneth William Batchelor, who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Marion Elizabeth Scott
Notary Public
My commission expires 11/15/97

G1070-2

ASSIGNMENT

I, Stephen Vernon Frye, for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, Stephen Vernon Frye, hereunto set my hand and seal this 16 day of March, 1995.

Stephen Vernon Frye

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, Stephen V. Frye, who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Sharon Elizabeth Scott
Notary Public
My commission expires 11/15/97

RECEIVED 96 JUL 19 PM 4:33

G1070-2

ASSIGNMENT

I, Robert A. Mook, Jr., for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, Robert A. Mook, Jr., hereunto set my hand and seal this 16 day of March, 1995.

R A Mook Jr

Robert A. Mook, Jr.,

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, Robert A. Mook, Jr., who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Sharon Elizabeth Scott

Notary Public
My commission expires 11/15/97

REEL 7404 FRAME 0710

G1070-2

ASSIGNMENT

I, George F. Dorsey, Jr., for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, George F. Dorsey, Jr., hereunto set my hand and seal this 16 day of March, 1995.

George F. Dorsey, Jr.

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, George F. Dorsey, Jr., who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Notary Public
My commission expires 11/15/97

RECORDED
PATENT & TRADEMARK OFFICE

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EXHIBIT 2A

Corporate Name Change

Glaxo Inc.

to

Glaxo Wellcome Inc.

Express Mail Label No.:
EL395889738US

STATE OF NORTH CAROLINA

Department of The Secretary of State

I, **RUFUS L. EDMISTEN,** Secretary of State of the State of North Carolina, do hereby certify that the following is a listing of all changes in the corporate name of the corporation named below, insofar as disclosed by the records of this office:
Original name at date of incorporation or authorization:

GLAXO INC.

State of Incorporation: North Carolina
Date of Incorporation or Authorization: 29 May 1985

Name Changes

Name change was effected by

Document and date filed or issued:	Name changed to:
Articles of Amendment filed 05 May 1995	**Glaxo Wellcome Inc.**

I FURTHER CERTIFY that this certificate is in compliance with North Carolina General Statute §55-4-05 and may be recorded in the office of the Register of Deeds in the same manner as deeds, the former name of the corporation appearing in the "Grantor" index and the amended name of the corporation appearing in the "Grantee" index.

IN WITNESS WHEREOF, *I have hereunto set my hand and affixed my official seal at the City of Raleigh, this 24th day of May, 1995.*

Rufus L. Edmisten

Secretary of State

EXHIBIT 2B

Articles of Merger

Between Glaxo Wellcome Inc.

And

SmithKline Beecham Corporation

Express Mail Label No.:
EL395889738US

C O M M O N W E A L T H O F P E N N S Y L V A N I A

D E P A R T M E N T O F S T A T E

APRIL 05, 2001

TO ALL WHOM THESE PRESENTS SHALL COME, GREETING:

SMITHKLINE BEECHAM CORPORATION

I, Kim Pizzingrilli, Secretary of the Commonwealth of Pennsylvania do hereby certify that the foregoing and annexed is a true and correct photocopy of Articles of Merger restating the Articles of Incorporation in their entirety

which appear of record in this department

IN TESTIMONY WHEREOF, I have hereunto set my hand and caused the Seal of the Secretary's Office to be affixed, the day and year above written.

Kim Pizzingrilli

Secretary of the Commonwealth

DPOS

RETURN TO CSC

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Filed with the Department of State on

Secretary of the Commonwealth JK

ARTICLES OF MERGER-DOMESTIC BUSINESS CORPORATION

DSCB:15-1926 (Rev 90)

In compliance with the requirements of 15 Pa.C.S. § 1926 (relating to articles of merger or consolidation), the undersigned iness corporations, desiring to effect a merger, hereby state that:

The name of the corporation surviving the merger is: SmithKline Beecham Corporation

(Check and complete one of the following):

X The surviving corporation is a domestic business corporation and the (a) address of its current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a) One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 Phila.
Number and Street City State Zip County

(b) c/o:
Name of Commercial Registered Office Provider County

For a corporation represented by a commercial registered office provider, the county in (b) shall be deemed the county in which the corporation is located for venue and official publication purposes.

___ The surviving corporation is a qualified foreign business corporation incorporated under the laws of ___ and the (a) address of its current registered office in this Commonwealth or (b) name of its commercial registered office provider and the county of venue is (the Department is hereby authorized to correct the following information to conform to the records of the Department):

(a)
Number and Street City State Zip County

(b) c/o:
Name of Commercial Registered Office Provider County

For a corporation represented by a commercial registered office provider, the county in (b) shall be deemed the county in which the corporation is located for venue and official publication purposes.

___ The surviving corporation is a nonqualified foreign business corporation incorporated under the laws of ___ and the address of its principal office under the laws of such domiciliary jurisdiction is:

Number and Street City State Zip

3. The name and the address of the registered office in this Commonwealth or name of its commercial registered office provider and the county of venue of each other domestic business corporation and qualified foreign business corporation which is a party to the plan of merger are as follows:

Name of Corporation	Address of Registered Office or Name of Commercial Registered Office Provider	County
Glaxo Wellcome Inc.	CT Corporation System	Philadelphia

THIS IS A TRUE COPY OF
THE ORIGINAL SIGNED
DOCUMENT FILED WITH
THE DEPARTMENT OF STATE

DSCB:15-1926 (Rev 90)-2

4. (Check, and if appropriate complete, one of the following):

___The plan of merger shall be effective upon filing these Articles of Merger in the Department of State.

_x_The plan of merger shall be effective on: March 31, 2001 (Date) at 11:30 p.m. (Hour)

5. The manner in which the plan of merger was adopted by each domestic corporation is as follows:

Name of Corporation	Manner of Adoption
SmithKline Beecham Corporation	Adopted by the directors and shareholders pursuant to 15 Pa.C.S. § 1924(a).

6. (Strike out this paragraph if no foreign corporation is a party to the merger). The plan was authorized, adopted or approved, as the case may be, by the foreign business corporation (or each of the foreign business corporations) party to the plan in accordance with the laws of the jurisdiction in which it is incorporated.

7. (Check, and if appropriate complete, one of the following):

_x_The plan of merger is set forth in full in Exhibit A attached hereto and made a part hereof.

___Pursuant to 15 Pa.C.S. § 1901 (relating to omission of certain provisions from filed plans) the provisions, if any, of the plan of merger that amend or constitute the operative Articles of Incorporation of the surviving corporation as in effect subsequent to the effective date of the plan are set forth in full in Exhibit A attached hereto and made a part hereof. The full text of the plan of merger is on file at the principal place of business of the surviving corporation, the address of which is:

Number and Street ____ City ____ State ____ Zip ____ County

IN TESTIMONY WHEREOF, the undersigned corporation or each undersigned corporation has caused these Articles of Merger to be signed by a duly authorized officer thereof this _____ day of March, 2001.

SMITHKLINE BEECHAM CORPORATION
(Name of Corporation)

BY: Donald F Parman
(Signature)

TITLE: Donald F. Parman, Secretary

GLAXO WELLCOME INC.
(Name of Corporation)

BY: Paul A. Holcombe Jr
(Signature)

TITLE: Paul A. Holcombe, Jr., Secretary

PLAN OF MERGER

between

SMITHKLINE BEECHAM CORPORATION

and

GLAXO WELLCOME INC.

PLAN OF MERGER approved on March 29, 2001 by SmithKline Beecham Corporation, a business corporation incorporated under the laws of the Commonwealth of Pennsylvania ("GSK"), and by resolution adopted by its Board of Directors on said date, and approved on March 28, 2001 by Glaxo Wellcome Inc., a business corporation formed under the laws of the State of North Carolina ("GWI"), and by resolutions adopted by its Board of Directors on said date.

1. Pursuant to the provisions of the Business Corporation Law of 1988 of the Commonwealth of Pennsylvania (the "PBCL") and the provision of the North Carolina Business Corporation Act (the "NCBCA"), GSK and GWI shall be merged with and into a single corporation, to wit, GSK, which shall be the surviving Pennsylvania corporation under the name "SmithKline Beecham Corporation" pursuant to the provisions of the PBCL (the "surviving corporation"). As the "terminating corporation" GWI shall cease to exist at the effective date of the merger in accordance with the provisions of the NCBCA.

2. From and after the effective time of the merger the Amended and Restated Articles of GSK set forth in Exhibit A attached hereto shall be the Articles of Incorporation of said surviving corporation and shall continue in full force and effect until amended and changed in the manner prescribed by the provisions of the PBCL.

3. From and after the effective time of the merger in the jurisdiction of its organization, the bylaws as set forth in Exhibit B attached hereto, shall be the bylaws of said surviving corporation and shall continue in full force and effect until changed, altered, or amended as therein provided and in the manner prescribed by the provisions of the BCL.

4. Upon the effective date of the merger the directors and officers as set forth in Exhibit C attached hereto, shall be the members of the first Board of Directors and the first officers of the surviving corporation, all of whom shall hold their directorships and offices until the election and qualification of their respective successors or until their tenure is otherwise terminated in accordance with the bylaws of the surviving corporation.

5. The 483,238 issued and outstanding shares of common stock of the terminating corporation immediately prior to the effective date of merger shall, upon the effective date of the merger, be converted into 624 shares of common stock of the surviving corporation. The 131,000,867 issued and outstanding shares of common stock of the surviving corporation immediately prior to the effective date of merger shall, upon the effective date of the merger, be converted into 376 shares of common stock of the surviving corporation. Neither the terminating company nor the surviving company has issued and outstanding any equity securities or securities, agreements or instruments convertible into or exercisable for equity securities other than the shares of common stock referred to in this Section 5.

6. In the event that this Plan of Merger shall have been fully approved and adopted on behalf of (i) the terminating corporation in the manner prescribed by the provisions of the NCBCA, and, (ii) the surviving corporation in accordance with the provisions of the PBCL, and the merger of the terminating corporation with and into the surviving corporation shall have been duly authorized in accordance with the provisions of said NCBCA and PBCL, the terminating corporation and the surviving corporation hereby stipulate that they will cause to be executed and filed and/or recorded any document or documents prescribed by the laws of the Commonwealth of Pennsylvania and the laws of the State of North Carolina and they will cause to be performed all necessary acts therein and elsewhere to effectuate the merger.

7. Any officer of the terminating corporation and any officer of the surviving corporation are hereby authorized to execute the Articles of Merger on behalf of said corporations, respectively, in conformity with the provisions of the PBCL; and the Board of Directors and the proper officers of the terminating corporation and of the surviving corporation, respectively, are hereby authorized, empowered, and directed to do any and

all acts and things, and to make, execute, deliver, file and/or record any and all instruments, papers, and documents which shall be or become necessary, proper, or convenient to carry out or put into effect any of the provisions of this Plan of Merger or the merger herein provided for. The effective time of this Plan of Merger and of the merger therein provided for shall, insofar as the provisions of the PBCL shall govern the same, be March 31, 2001 at 11:30 p.m.

IN WITNESS WHEREOF, the parties intending to be legally bound hereto have executed this Plan of Merger effective as of the date first above written.

SMITHKLINE BEECHAM CORPORATION

By: Donald F. Parman
Name: Donald F. Parman
Title: Secretary

GLAXO WELLCOME INC.

By: Paul A. Holcombe, Jr.
Name: Paul A. Holcombe, Jr.
Title: Secretary

Exhibit A

SMITHKLINE BEECHAM CORPORATION

Amended and Restated Articles of Incorporation

FIRST: The name of the corporation (hereinafter called the "Corporation") is SmithKline Beecham Corporation.

SECOND: The location and post office address of the current registered office of the Corporation in the Commonwealth of Pennsylvania is One Franklin Plaza, Philadelphia, Pennsylvania 19102.

THIRD: The Corporation is incorporated under the Business Corporation Law of 1988. The Corporation shall have unlimited power to engage in and to do any lawful act concerning any and all business for which corporations may be incorporated under the Pennsylvania Business Corporation Law, including but not limited to buying, selling and otherwise dealing with drugs, medicines, chemicals, foods, cosmetics, toiletries, and all supplies, devices and services used by the health professions, or the drug trade.

FOURTH: The aggregate number of shares which the Corporation shall have authority to issue is 3,000 shares divided into 2,000 shares of common stock with a par value of one dollar per share, and 1,000 shares of preferred stock without par value.

FIFTH: The Board of Directors of the Corporation shall have the power, by resolution duly adopted, to issue from time to time, in whole or in part, the authorized and unissued shares into classes or series, or both, and to determine for any such class or series its voting rights, designations, preferences, limitations and any special rights.

SIXTH: Any actions required or permitted to be taken at a meeting of shareholders may be taken without a meeting pursuant to Section 1766 of the Business Corporation Law of 1988, as the same may be amended and supplemented, upon the

written consent of shareholders who would have been entitled to cast the minimum number of votes that would be necessary to authorize the action at a meeting at which all shareholders entitled to vote thereon were present and voting

SEVENTH: Shareholders of the Corporation shall not be entitled to cumulative voting rights in elections of Directors.

EIGHTH: The personal liability of the directors of the Corporation is limited to the fullest extent permitted by the provisions of the Business Corporation Law of 1988 as the same may be amended and supplemented.

NINTH: The effective time and date of these Amended and Restated Articles of Incorporation shall be 11:30 p.m. on March 31, 2001.

Exhibit B

SMITHKLINE BEECHAM CORPORATION

BY-LAWS

ADOPTED JUNE 29, 1929, WITH ALL
AMENDMENTS TO AND INCLUDING MARCH 31, 2001

ARTICLE I.
SHAREHOLDERS' MEETINGS

SECTION 1. ANNUAL MEETINGS. The annual meeting of the shareholders of this Corporation shall be held at such time and place and on such date as the Board of Directors may designate, at which time the shareholders shall elect the Board of Directors.

SECTION 2. SPECIAL MEETINGS. Special meetings of the shareholders may be called at any time by the President, or the Board of Directors or the holders of not less than one-fifth of all the shares outstanding and entitled to vote at the particular meeting. At any time upon the request of any person or persons who shall have duly called a special meeting, it shall be the duty of the Secretary to fix the date of the meeting, which shall be not more than sixty days after the receipt of the request.

SECTION 3. NOTICES. A written notice of every meeting of shareholders, specifying the place, day and hour of the meeting, shall be mailed by the Secretary at least ten days prior to the meeting, to each shareholder entitled to vote thereat, at his address appearing on the books of the Corporation or supplied by him to the Corporation for the purpose of notice. In the case of special meetings, the notice shall state the general nature of the business to be transacted thereat and no business shall be transacted at special meetings except that indicated in the notice.

SECTION 4. QUORUM. The presence, in person or by proxy, of the holders of a majority of the issued and outstanding shares entitled to vote at the meeting shall constitute a quorum at any meeting of the shareholders; but if the meeting cannot be organized because a quorum has not attended, those present may adjourn the meeting from time to time, provided, however, that in the case of any meeting called for the election of directors, those who attend the second of such adjourned meetings, although less than a quorum, shall, nevertheless, constitute a quorum for the purpose of electing directors.

SECTION 5. RECORD DATE. The Board of Directors may fix a time, not more than fifty days prior to the date of any meeting of shareholders, or the date fixed for

the payment of any dividend or distribution, or the date of the allotment of rights or the date when any change or conversion or exchange of shares will be made or go into effect, as a record date of the determination of the shareholders entitled to notice or, or to vote at, any such meeting, or entitled to receive any such allotment of rights, or to exercise the rights in respect to any such change, conversion or exchange of shares. In such case, only such shareholders as shall be shareholders of record on the date so fixed shall be entitled to notice of, or to vote, at, such meeting or to receive payment of such dividend, or to receive such allotment or rights, or to exercise such rights, as the case may be, notwithstanding any transfer of any shares on the books of the Corporation after any record date fixed, as aforesaid.

ARTICLE II.
DIRECTORS

SECTION 1. NUMBER. The business of this Corporation shall be managed by a Board of Directors which shall consist of five members. The Board of Directors shall have power to increase or decrease the number of directors and to fill any vacancies in their number, including vacancies resulting from any increase in the number of directors. Directors need not be shareholders.

SECTION 2. AGE QUALIFICATION. Except as otherwise specifically provided by the Board of Directors, (a) no person shall be elected a director after reaching 69 years of age, (b) no person who has been an officer or full-time employee of the Corporation, or any subsidiary thereof, other than President or Chairman of the Board, shall be elected a director after reaching 65 years of age and (c) no person shall be elected Chairman of the Board after reaching 65 years of age.

SECTION 3. TERM. Directors shall hold office until the next annual election and until their successors are elected and qualified.

SECTION 4. REGULAR MEETINGS. The Board of Directors shall meet at the general office of the Corporation as soon as practicable after the annual meeting of shareholders for the purpose of organization, the election of officers and the transaction of such other business as shall come before the meeting. Other regular meetings shall be held at such times as may be fixed by resolution of the Board of Directors.

SECTION 5. SPECIAL MEETINGS. Special meetings of the Board may be called by the Chairman of the Board, the President, or the Secretary and shall be called at the request in writing of three or more directors.

SECTION 6. NOTICES. No notice of the organization meeting or of regular meetings of the Board need be given. Notice of the place, day and hour of each special meeting and the general nature of the business to be transacted shall be given by the Secretary to each director either by written notice mailed at least two days before the meeting or by notice given personally or by telephone or telegraph at least 24 hours before the meeting. Notice of any meeting may be waived.

SECTION 7. QUORUM. A majority of the directors in office shall constitute a quorum for the transaction of business. Should there be no quorum, the members present may adjourn from time to time until a quorum is in attendance.

SECTION 8. COMPENSATION. Directors shall receive such compensation for their services as may, from time to time, be fixed by resolution of the Board of Directors.

SECTION 9. PARTICIPATION IN MEETING BY COMMUNICATIONS EQUIPMENT. One or more directors may participate in a meeting of the Board or a committee of the Board by means of conference telephone or similar communications equipment be means of which will persons participating in the meeting can hear each other.

ARTICLE III.
EXECUTIVE COMMITTEE

SECTION 1. ELECTION. The Board of Directors may elect from their members each year an Executive Committee which shall include the Chairman of the Board, the President and such additional members, not less than one, as the Board of Directors may from time to time determine. The Chairman of the Board shall be Chairman of the Executive Committee.

SECTION 2. POWERS AND QUORUM. The Executive Committee shall have power to manage the general business and affairs of the Corporation, subject always to the superior direction and control of the Board of Directors. All persons dealing with the Corporation shall have the right to rely upon any resolution adopted by the Executive Committee to the same extent as if it had been duly adopted by the Board of Directors. Two members of the Executive Committee shall constitute a quorum for the transaction of business.

SECTION 3. MEETINGS AND NOTICES. The Executive Committee, by resolution, may fix regular meeting dates, of which no notice need be given to members of the Committee. Special meetings may be held at the call of the Chairman of the Executive Committee, or in his absence, at the call of the President. Notice of the place, day and hour of each special meeting shall be given to each member at least 24 hours before the meeting.

SECTION 4. BOARD SUBMISSION. All action taken by the Executive Committee shall be reported to the Board not later than the next succeeding regular meeting of the Board.

SECTION 5. ALTERNATES. In the absence or disqualification of any member of the Executive Committee, the member or members thereof present at any meeting and not disqualified from voting, whether or not he or they constitute a quorum, may unanimously appoint another director to act at the meeting in the place of any such absent or disqualified member.

ARTICLE IV.
OFFICERS

SECTION 1. ELECTION, POWERS AND DUTIES. The Board of Directors shall have authority to elect the following officers:

(a) A Chairman who shall preside at all meetings of the Board of Directors and shareholders.

(b) A President who shall be the Chief Executive officer of the Corporation. He shall be responsible for the overall management of the business and affairs of the Corporation and shall perform his duties subject to the direction and control of the Board of Directors. In the absence of the Chairman of the Board, the President shall preside at meetings of the Board and shareholders.

(c) One or more Vice Chairmen, Vice Presidents, a Secretary, a Treasurer and such additional officers as the Board of Directors may deem advisable.

Persons elected to the offices of Chairman and President shall be members of the Board and may attend meetings of all committees of the Board and meetings of management committees. The Chairman shall be available to other officers of the Corporation for consultation and advice.

All officers shall perform such duties, shall have such powers and shall be compensated in such manner as these by-laws may provide or as the Board of Directors may prescribe, and shall be removable by the Board at will.

SECTION 2. PLURALITY OF OFFICERS. A person may occupy more than one office except that the offices of President and Secretary may not be held by the same person.

ARTICLE V.
LIABILITY OF DIRECTORS

A director of the Corporation shall not be personally liable, as such, for monetary damages for any action taken, or any failure to take any action, on or after January 27, 1987 unless (a) the director has breached or failed to perform the duties of his office under Section 1721 of the Pennsylvania Business Corporation Law and the breach or failure to perform constitutes self-dealing, willful misconduct or recklessness. The provisions of this Article V shall not apply to the responsibility or liability of a director pursuant to any criminal statute or the liability of a director for the payment of taxes pursuant to local, state or Federal law. Any repeal, amendment, or modification of this Article shall be prospective only and shall not increase, but may decrease, a director's liability with respect to actions or failures to act occurring prior to such change.

ARTICLE VI.
INDEMNIFICATION

SECTION 1. INDEMNIFICATION OF DIRECTORS AND OFFICERS. The Corporation shall indemnify any director or officer or employee or agent of the Corporation or any of its subsidiaries who was or is an "authorized representative" of the Corporation (which shall mean, for the purpose of this Article, a director or officer or employee of the Corporation or any of its subsidiaries, or a person serving at the request of the Corporation as a director, officer, partner, fiduciary or trustee of another corporation, partnership, joint venture, trust, employee benefit plan or other enterprise) and who was or is a "party"(which shall include for purposes of this Article the giving of testimony or similar involvement) or is threatened to be made a party to any "proceeding" (which shall mean for purposes of this Article any threatened, ending or completed action, suit, appeal or other proceeding of any nature, whether civil criminal, administrative or investigative, whether formal or informal, and whether brought by or in the right of the Corporation, its shareholders or otherwise) by reason of the fact that such person was or is an authorized representative of the Corporation to the fullest extent permitted by law, including without limitation indemnification against expenses (which shall include for purposes of this Article attorneys' fees and disbursements), damages, punitive damages, judgments, penalties, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such proceeding unless the act or failure to act giving rise to the claim is finally determined by a court to have constituted willful misconduct or recklessness. If an authorized representative is not entitled to indemnification in respect of a portion of any liabilities to which such person may be subject, the Corporation shall nonetheless indemnify such person to the maximum extent for the remaining portion of the liabilities.

SECTION 2. ADVANCEMENT OF EXPENSES. The Corporation shall pay the expenses (including attorneys' fees and disbursements) actually and reasonably incurred in defending a proceeding on behalf of any person entitled to indemnification under Section 1 of this Article in advance of the final disposition of such proceeding upon receipt of an undertaking by or on behalf of such person to repay such amount if it shall ultimately be determined that such person is not entitled to be indemnified by the Corporation as authorized in this Article. The financial ability of such authorized representative to make such repayment shall not be prerequisite to the making of an advance.

SECTION 3. EMPLOYEE BENEFIT PLANS. For purposes of this Article, the Corporation shall be deemed to have requested an officer, director, employee or agent to serve as a fiduciary with respect to an employee benefit plan where the performance by such person of duties to the Corporation also imposes duties on, or otherwise involves services by, such person as a fiduciary with respect to the plan; excise taxes assessed on an authorized representative with respect to any transaction with an employee benefit plan shall be deemed "fines"; and action taken or omitted by such person with respect to an employee benefit plan in the performance of duties for a purpose reasonably believed

to be in the interest of the participants and beneficiaries of the plan shall be deemed to be for a purpose which is not opposed to the best interests of the Corporation.

SECTION 4. SECURITY OF INDEMNIFICATION OBLIGATIONS. To further effect, satisfy or secure the indemnification obligations provided herein or otherwise, the Corporation may maintain insurance, obtain a letter of credit, act as self-insurer, create a reserve, trust, escrow, cash collateral or other fund or account, enter into indemnification agreements, pledge or grant a security interest in any assets or properties of the Corporation, or use any other mechanism or arrangement whatsoever in such amounts, at such costs, and upon such other terms and conditions as the Board of Directors shall deem appropriate.

SECTION 5. RELIANCE UPON PROVISIONS. Each person who shall act as an authorized representative of the Corporation shall be deemed to be doing so in reliance upon the rights of indemnification provided by this Article.

SECTION 6. AMENDMENT OR REPEAL. Notwithstanding anything contained in Article IX of these by-laws, this Article shall not be repealed or amended or modified to limit the indemnification rights provided hereunder except by action of the shareholders. All rights to indemnification under this Article shall be deemed a contract between the Corporation and the person entitled to indemnification under this Article pursuant to which the Corporation and each such person intend to be legally bound. Any repeal, amendment of modification hereof shall be prospective only and shall not limit, but may expand, any rights or obligations in respect of any proceeding whether commenced prior to or after such change to the extent such proceeding pertains to actions or failures to act occurring prior to such change.

SECTION 7. SCOPE OF ARTICLE. The indemnification, as authorized by this Article, shall not be deemed exclusive of any other rights to which those seeking indemnification or advancement of expenses may be entitled under statute, agreement, vote of shareholders or disinterested directors or otherwise, both as to action in such person's official capacity and as to action in another capacity while holding that office. The indemnification and advancement of expenses provided by, or granted pursuant to, this Article shall continue as to a person who has ceased to be an officer, director, employee or agent in respect of matters arising prior to such time, and shall inure to the benefit of the heirs, executors and administrators of such person.

ARTICLE VII.
OFFICE AND SEAL

SECTION 1. OFFICE AND RECORDS. The general office of the Corporation, with the books and papers thereto belonging, shall be at Philadelphia, Pennsylvania, in such location as any from time to time be fixed by the Board of Directors.

SECTION 2. SEAL. The seal of this Corporation shall bear the name of the Corporation and the State and the year of its incorporation. The seal shall be in the

custody of the Secretary and shall be affixed by the Secretary or, in his absence, by an Assistant Secretary, unless otherwise provided by resolution of the Board of Directors.

ARTICLE VIII.
STOCK

Share certificates shall be issued to all shareholders. Every share certificate shall be signed by the Chairman of the Board, President or Vice President and the Secretary or Assistant Secretary or the Treasurer or Assistant Treasurer, or such other officers of the Board of Directors may direct and sealed with the corporate seal which may be a facsimile, engraved or printed. Where the certificates are signed by a transfer agent or a registrar, the signature of any officer of the Corporation appearing thereon may be a facsimile, engraved or printed. The fact that an officer whose signature, manual or in facsimile, appears on stock certificates, issued or on hand, shall cease to be an officer of the Corporation shall not invalidate any of such certificates.

ARTICLE IX.
AMENDMENTS

These by-laws may be altered, amended, added to or repealed at any meeting of shareholders by vote of a majority of shares of stock represented at the meeting, provided notice of the change be given in the notice of the meeting; or, except as provided in Articles V and VI, they may be altered, amended, added to or repealed at any meeting of the Board of Directors by vote of a majority of the directors in office, provided notice of the change be given in the manner required for notices of special meetings.

Exhibit C

SMITHKLINE BEECHAM CORPORATION

Directors and Officers

Directors

Robert A. Ingram
Tadataka Yamada
David M. Stout
Michael Corrigan
Paul A. Holcombe, Jr.

Officers

Name	Office(s)
Robert A. Ingram	Chairman
Tadataka Yamada	Vice Chairman
David M. Stout	President
Paul A. Holcombe, Jr.	Senior Vice President and General Counsel – U.S.
Michael Corrigan	Senior Vice President, Finance – U.S. Pharmaceuticals
Richard Edge	Treasurer
Audrey Klijian	Assistant Treasurer
Richard Gossin	Assistant Treasurer
Donald F. Parman	Vice President and Secretary
Teresa M. Hechmer	Assistant Secretary
Sandra C. Henderson	Assistant Secretary
Charles M. Kinzig	Assistant Secretary
David J. Levy	Assistant Secretary
William J. Mosher	Assistant Secretary
Christopher A. Sidoti	Assistant Secretary

EXHIBIT 3

FDA Approval Letter for dutasteride
soft gelatin capsules, 0.5mg
NDA21-319

Express Mail Label No.:
EL395889738US

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-319

GlaxoSmithKline
Attention: Munir Abdullah, Ph.D.
Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. Abdullah:

Please refer to your new drug application (NDA) dated December 21, 2000, received December 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dutasteride soft gelatin capsules, 0.5 mg.

We acknowledge receipt of your submissions dated January 3 and 26, March 1, April 20, May 9, 10, 15 and 24, June 15 and 25, July 2, 9, 13, 16, 20, and 26, August 7, 14 and 23, September 4, 7, 19 and 27, October 1, 4, 9, 11, 15 and 24, and November 2, 8, 13, 15, 16, 19 and 20, 2001.

This new drug application provides for the use of dutasteride soft gelatin capsules 0.5 mg for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate gland.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), and the draft labeling (carton and container submitted on November 16, 2001). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-319." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated November 15, 2001. This commitment is listed below.

Conduct a study to investigate *in vitro* metabolism using therapeutically relevant dutasteride concentrations to characterize the metabolic pathways.

Protocol submission:	Within 1 month of the date of this letter
Study start:	Within 3 months of the date of this letter
Final report submission:	Within 6 months of the start of the study

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Florence Houn
11/20/01 04:13:37 PM

EXHIBIT 4

Approved Product Information / Package Insert for
Dutasteride soft gelatin capsules, 0.5mg
NDA21-319

PRODUCT INFORMATION

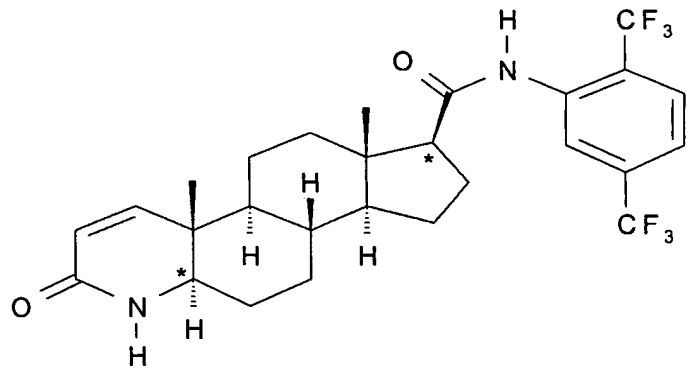
TRADENAME

(dutasteride)

Soft Gelatin Capsules

DESCRIPTION: TRADENAME (dutasteride) is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5α-reductase (5AR), an intracellular enzyme that converts testosterone to 5α-dihydrotestosterone (DHT).

Dutasteride is chemically designated as (5α, 17β)-N-{2, 5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5 with the following structural formula:



Dutasteride is a white to pale yellow powder with a melting point of 242 to 250°C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL) and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

TRADENAME Soft Gelatin Capsules for oral administration contain 0.5 mg of the active ingredient dutasteride in yellow capsules with red print. Each capsule contains 0.5 mg dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified BSE-free bovine sources), glycerin, and ferric oxide (yellow). The soft gelatin capsules are printed with edible red ink.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: ***Mechanism of Action:*** Dutasteride inhibits the conversion of testosterone to 5α-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5α-reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5α-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.

Effect on DHT and Testosterone: The maximum effect of daily doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with dutasteride 0.5 mg/day for 1 year, the median decrease in serum DHT was 94%. The median increase in serum testosterone was 19% but remained within the physiologic range.

In BPH patients treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the dutasteride group compared with placebo (784 and 5793 pg/g, respectively, $p<0.001$). Mean prostatic tissue concentrations of testosterone were significantly higher in the dutasteride group compared with placebo (2073 and 93 pg/g, respectively, $p<0.001$).

Adult males with genetically inherited type 2 5α-reductase deficiency also have decreased DHT levels. These 5α-reductase deficient males have a small prostate gland throughout life and do not develop BPH. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to 5α-reductase deficiency have been observed in these individuals.

Other Effects: Plasma lipid panel and bone mineral density were evaluated following 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy x-ray absorptiometry (DEXA) compared with either placebo or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically significant changes in

adrenal hormone responses to ACTH stimulation were observed in a subset population (n = 13) of the one-year healthy volunteer study.

Pharmacokinetics:

Absorption: Following administration of a single 0.5-mg dose of a soft gelatin capsule, time to peak serum concentrations (Tmax) of dutasteride occurs within 2 to 3 hours. Absolute bioavailability in five healthy subjects is approximately 60% (range 40% to 94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10% to 15%. This reduction is of no clinical significance.

Distribution: Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%).

In a study of healthy subjects (n = 26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months, 11.5% of serum dutasteride concentrations partitioned into semen.

Metabolism and Elimination: Dutasteride is extensively metabolized in humans. While not all metabolic pathways have been identified, in vitro studies showed that dutasteride is metabolized by the CYP3A4 isoenzyme to 2 minor mono-hydroxylated metabolites. Dutasteride is not metabolized in vitro by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6 at 2000 ng/mL (50-fold greater than steady-state serum concentrations). In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4′-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride) and 2 minor metabolites (6,4′-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is not known. In vitro, 4′-hydroxydutasteride and 1, 2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of human 5AR. The activity of 6β-hydroxydutasteride is comparable to that of dutasteride.

Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~ 2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range 5% to 97%).

The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state. The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Special Populations: ***Pediatric:*** Dutasteride pharmacokinetics have not been investigated in subjects less than 18 years of age.

Geriatric: No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5-mg dose of dutasteride. In this single-dose study, dutasteride half-life increased with age (approximately 170 hours in men 20 to 49 years of age, approximately 260 hours in men 50 to 69 years of age, and approximately 300 hours in men over 70 years of age). Of 2166 men treated with dutasteride in the 3 pivotal studies, 60% were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

Gender: TRADENAME is not indicated for use in women (see WARNINGS and PRECAUTIONS). The pharmacokinetics of dutasteride in women have not been studied.

Race: The effect of race on dutasteride pharmacokinetics has not been studied.

Renal Impairment: The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5-mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic Impairment: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients (see PRECAUTIONS: Use in hepatic impairment).

Drug Interactions:

In vitro drug metabolism studies reveal that dutasteride is metabolized by human cytochrome P450 isoenzyme CYP3A4. In a human mass balance analysis (n = 8), dutasteride was extensively metabolized. Less than 20% of the dose was excreted unchanged in the feces. No clinical drug interaction studies have been performed to evaluate the impact of CYP3A4 enzyme inhibitors on

dutasteride pharmacokinetics. However, based on the in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin. Dutasteride is not metabolized in vitro by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6 at 2000 ng/mL (50-fold greater than steady-state serum concentrations).

Clinical drug interaction studies have shown no pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin, terazosin, warfarin, digoxin, and cholestyramine (see PRECAUTIONS: Drug Interactions)

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/mL, 25 times greater than steady-state serum concentrations in humans.

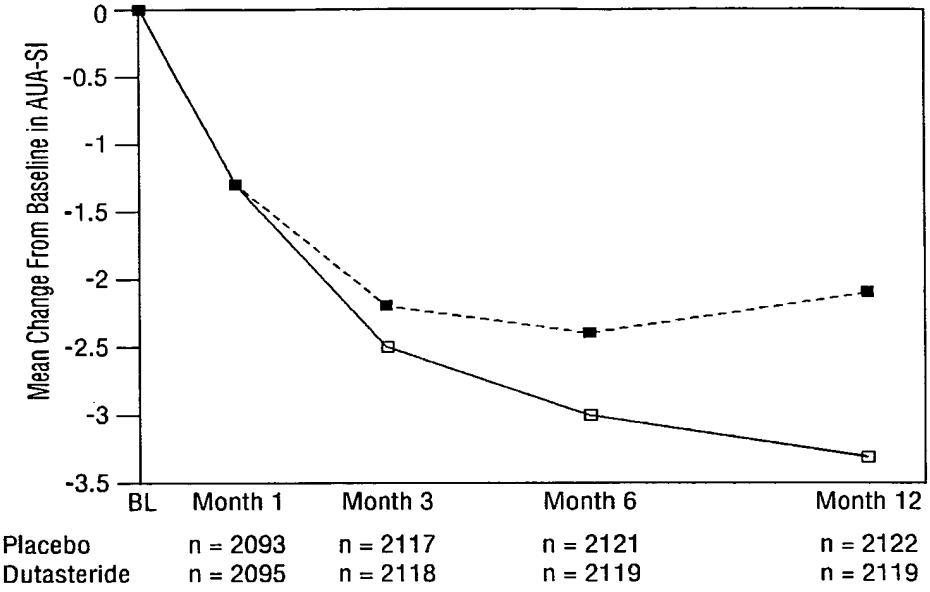
CLINICAL STUDIES: Dutasteride 0.5 mg/day (n =2166) or placebo (n = 2158) was evaluated in male subjects with BPH in three 2-year multicenter, placebo-controlled, double-blind studies, each with 2-year open-label extensions. Data from the first 12 months of the trials are presented. More than 90% of the study population was Caucasian. Subjects were at least 50 years of age with BPH diagnosed by medical history and physical examination, including enlarged prostate (≥30 cc) and BPH symptoms that were moderate to severe according to the American Urological Association Symptom Index (AUA-SI). Most of the 4324 subjects randomly assigned to receive either dutasteride or placebo completed the first full year of treatment (82% and 81%, respectively).

Effect on Symptom Scores: Symptoms were quantified using the AUA-SI, a questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) by rating on a 0 to 5 scale for a total possible score of 35. The baseline AUA-SI score across the three studies was approximately 17 units in both treatment groups.

Subjects receiving dutasteride achieved statistically significant improvement in symptoms versus placebo by Month 3 in one study, and by Month 12 in the other two pivotal studies. At Month 12, the mean decrease from baseline in AUA-SI symptom scores across the three studies pooled was -3.3 units for dutasteride and -2.1 units for placebo with a mean difference between the two treatment groups of -1.2 (range, -1.1 to -1.5 units in each of the three studies, $p<0.001$) and was consistent across the three studies. The differences between active treatment and placebo were larger in the sub-population of subjects with baseline prostate volumes of at least 40 cc.

Figure 1: AUA Symptom Score* Change from Baseline

Pivotal Studies Pooled



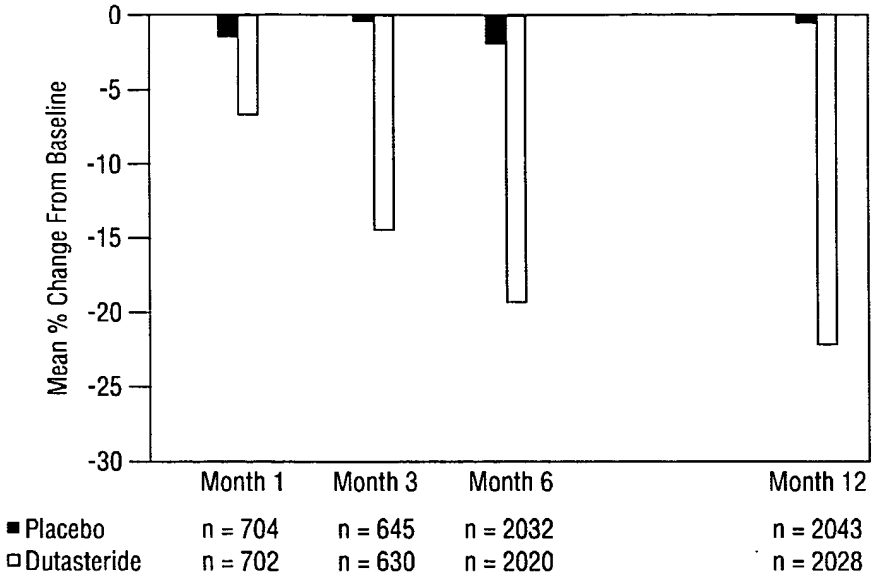
*AUA SI score ranges from 0 to 35.

Effect on Prostate Volume: A prostate volume of at least 30 cc measured by transrectal ultrasound was required for study entry. The mean prostate volume at study entry was approximately 54 cc.

Statistically significant differences (dutasteride versus placebo) were noted at the earliest post-treatment prostate volume measurement in each study (Month 1, Month 3, or Month 6) and continued through Month 12. At Month 12, the mean percent decrease in prostate volume across the three studies pooled was -22.2% for dutasteride and -0.5% for placebo; the mean difference (dutasteride minus placebo) was -21.7% (range, -21.1% to -22.5% in each of the three studies, $p<0.001$).

Figure 2: Prostate Volume Percent Change from Baseline

Pivotal Studies Pooled

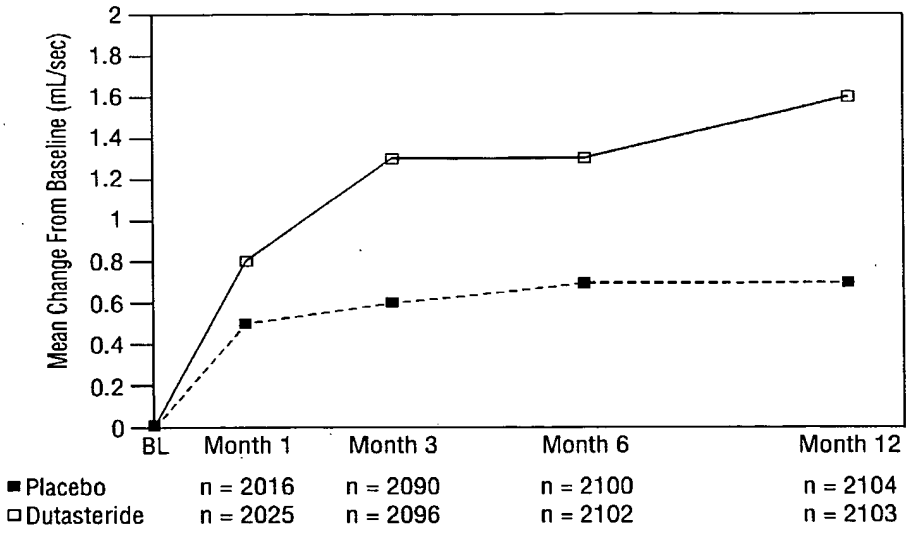


Effect on Maximum Urine Flow Rate: A mean peak urine flow rate (Qmax) of ≤15 mL/sec was required for study entry. Baseline Qmax was approximately 10 mL/sec at baseline across the three pivotal studies.

Differences between the two groups were statistically significant from baseline at Month 3 in all three studies and were maintained through Month 12. At Month 12, the mean increase in Qmax across the three studies pooled was 1.6 mL/sec for dutasteride and 0.7 mL/sec for placebo; the mean difference (dutasteride minus placebo) was 0.9 mL/sec (range, 0.7 to 1.1 mL/sec in each of the three studies, $p<0.001$).

Figure 3: Qmax Change from Baseline

Pivotal Studies Pooled



Summary of Clinical Studies: The data from these studies showed improvement in BPH-related symptoms, decreased prostate volume, and increased maximum urinary flow rates with dutasteride treatment.

INDICATIONS AND USAGE: TRADENAME is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland.

CONTRAINDICATIONS: TRADENAME is contraindicated for use in women and children. TRADENAME is contraindicated for patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, or any component of the preparation.

WARNINGS:

Exposure of Women-Risk to Male Fetus: Dutasteride is absorbed through the skin. Therefore, women who are pregnant or may be pregnant should not handle TRADENAME Soft Gelatin Capsules because of the possibility of absorption of dutasteride and the potential risk of a fetal anomaly to a male fetus (see CONTRAINDICATIONS). In addition, women should use caution whenever handling TRADENAME Soft Gelatin Capsules.

PRECAUTIONS:

General: Lower urinary tract symptoms of BPH can be indicative of other urological diseases, including prostate cancer. Patients should be assessed to rule out other urological diseases prior to treatment with TRADENAME. Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5α-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

Blood Donation: Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Use in Hepatic Impairment: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of approximately 5 weeks at steady state, caution should be used in the administration of dutasteride to patients with liver disease.

Use with Potent CYP3A4 Inhibitors: Although dutasteride is extensively metabolized, no metabolically-based drug interaction studies have been conducted. The effect of potent CYP3A4 inhibitors has not been studied. Because of the potential for drug-drug interactions, care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir).

Effects on PSA and Prostate Cancer Detection: Digital rectal examinations, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with TRADENAME and periodically thereafter.

Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months of treatment and 50% following 6 and 12 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Therefore, for interpretation of serial PSAs in a man taking TRADENAME, a new baseline PSA concentration should be established after 3 to 6 months of treatment, and this new value should be used to assess potentially cancer-related changes in PSA. To interpret an isolated PSA value in a man treated with TRADENAME for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

Information for Patients: Physicians should instruct their patients to read the Information for Patient leaflet before starting therapy with TRADENAME and to reread it upon prescription renewal for new information regarding the use of TRADENAME.

TRADENAME Soft Gelatin Capsules should not be handled by a woman who is pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent

potential risk to a developing male fetus (see CONTRAINDICATIONS, and WARNINGS: Exposure Of Women—Risk To Male Fetus).

Physicians should inform patients that ejaculate volume might be decreased in some patients during treatment with TRADENAME. This decrease does not appear to interfere with normal sexual function. In clinical trials, impotence and decreased libido, considered by the investigator to be drug-related, occurred in a small number of patients treated with TRADENAME or placebo (5% and 3%, respectively, see ADVERSE REACTIONS).

Men treated with dutasteride should not donate blood until at least 6 months have passed following their last dose to prevent pregnant women from receiving dutasteride through blood transfusion (see PRECAUTIONS: Blood Donation).

Drug Interactions:

Caution should be used in administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors (see PRECAUTIONS: Use with Potent CYP3A4 Inhibitors).

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/mL, 25 times greater than steady-state serum concentrations in humans. In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein binding sites, nor do these model compounds displace dutasteride.

Digoxin: In a study of 20 healthy volunteers, TRADENAME did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Warfarin: In a study of 23 healthy volunteers, 3 weeks of treatment with TRADENAME 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time when administered with warfarin.

Alpha adrenergic blocking agents: In a single sequence, cross-over study in healthy volunteers, the administration of tamsulosin or terazosin in combination with TRADENAME had no effect on the steady-state pharmacokinetics of either alpha adrenergic blocker. The percent change in DHT concentrations was similar for TRADENAME alone compared with the combination treatment.

Calcium Channel Antagonists: In a population PK analysis, a decrease in clearance of dutasteride was noted when co-administered with the CYP3A4 inhibitors verapamil (-37%, n = 6) and diltiazem (-44%, n = 5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP34A inhibitor, was co-administered with dutasteride (+7%, n = 4).

Cholestyramine: Administration of a single 5-mg dose of TRADENAME followed 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal volunteers.

Other Concomitant Therapy: Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in the 3 Phase III pivotal efficacy studies receiving TRADENAME were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of TRADENAME and concurrent therapy when TRADENAME was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

Drug/Laboratory Test Interactions: Effects on PSA: PSA levels generally decrease in patients treated with TRADENAME as the prostate volume decreases. In approximately one-half of the subjects, a 20% decrease in PSA is seen within the first month of therapy. After 6 months of therapy, PSA levels stabilize to a new baseline that is approximately 50% of the pre-treatment value. Results of subjects treated with TRADENAME for up to two years indicate this 50% reduction in PSA is maintained. Therefore, a new baseline PSA concentration should be established after 3 to 6 months of treatment with TRADENAME (see PRECAUTIONS: Effects on PSA and Prostate Cancer Detection).

Hormone Levels: In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day (n = 26) resulted in no clinically significant change compared with placebo (n = 23) in sex hormone binding globulin, estradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4), and dehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dL, $p<0.003$) and thyroid-stimulating hormone (TSH) at 52 weeks (0.4 mcIU/mL, $p<0.05$). The median percentage changes from baseline within the dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for TSH at 52 weeks. In BPH patients treated with dutasteride in a large Phase III trial, there was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at 12 months.

Reproductive Function: The effects of dutasteride 0.5 mg/day on reproductive function were evaluated in normal volunteers aged 18 to 52 (n = 26) throughout 52 weeks of treatment. Semen characteristics were evaluated at 3 timepoints and indicated no clinically meaningful changes in sperm concentration, sperm motility, or sperm morphology. A 0.8 mL (25%) mean decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed at 52 weeks. These parameters remained within the normal range.

CNS Toxicity: In rats and dogs, repeated oral administration of dutasteride resulted in some animals showing signs of non-specific, reversible, centrally-mediated toxicity, without associated histopathological changes at exposure 425- and 315-fold the expected clinical exposure (of parent drug), respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: In a 2-year carcinogenicity study in B6C3F1 mice, at doses of 3, 35, 250, and 500 mg/kg/day for males and 3, 35, and 250 mg/kg/day for females. An increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (290-fold the expected clinical exposure to a 0.5 mg daily dose) in females only. Two of the three major human metabolites have been detected in mice. The exposure to these metabolites in mice is either lower than in humans or is not known.

In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and 53 mg/kg/day for males and 0.8, 6.3, and 15 mg/kg/day for females there was an increase in Leydig cell adenomas in the testes at 53 mg/kg/day (135-fold the expected clinical exposure). An increased incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/day (52-fold the expected clinical exposure) and 53 mg/kg/day in male rats. A positive correlation between proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5α-reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-testicular axis following 5α-reductase inhibition. At tumorigenic doses in rats, luteinizing hormone levels in rats were increased by 167%. In this study, the major human metabolites were tested for carcinogenicity at approximately 1 to 3 times the expected clinical exposure.

Mutagenesis: Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames test or an abbreviated Ames test.

Impairment of Fertility: Treatment of sexually mature male rats with dutasteride at doses of 0.05, 10, 50, and 500 mg/kg/day (0.1 to 110-fold the expected clinical exposure of parent drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility, reduced cauda epididymal sperm counts (at 50 and 500 mg/kg/day), reduced weights of the epididymis, prostate and seminal vesicles, and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery period. The 5α-reductase-related changes consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were no longer present at

recovery week 14 in the low-dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/mL) were detected in the serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/ day for 29 to 30 weeks.

In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption and feminization of male fetuses (decreased anogenital distance) at doses of ≥2.5 mg/kg/ day (2- to 10-fold the clinical exposure of parent drug in men). Fetal body weights were also reduced at ≥0.05 mg/kg/day in rats (<0.02-fold the human exposure).

Pregnancy: Pregnancy Category X (see CONTRAINDICATIONS). TRADENAME is contraindicated for use in women. TRADENAME has not been studied in women because preclinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male fetus carried by a woman exposed to dutasteride.

In an intravenous embryo-fetal development study in the rhesus monkey (12/group), administration of dutasteride at 400, 780, 1325, or 2010 ng/day on gestation days 20 to 100 did not adversely affect development of male external genitalia. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were observed in monkeys treated with the highest dose. Based on the highest measured semen concentration of dutasteride in treated men (14 ng/mL these doses represent 0.8 to 16 times (based on blood levels of parent drug) the potential maximum exposure of a 50-kg human female to 5 mL semen daily from a dutasteride-treated man, assuming 100% absorption. Dutasteride is highly bound to proteins in human semen (>96%), potentially reducing the amount of dutasteride available for vaginal absorption.

In an embryo-fetal development study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in feminization of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses (0.07- to 111-fold the expected male clinical exposure). An increase in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was observed at doses ≥2.5 mg/kg/day (15- to 111-fold the expected clinical exposure). Increased incidences of skeletal variations considered to be delays in ossification associated with reduced body weight were observed at doses of 12.5 and 30 mg/kg/day (56- to 111-fold the expected clinical exposure).

In an oral pre- and post natal development study in rats, dutasteride doses of 0.05, 2.5, 12.5, or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia (i.e., decreased anogenital distance, increased incidence of hypospadias, nipple development) of F1

generation male offspring occurred at doses ≥2.5 mg/kg/day (14- to 90-fold the expected clinical exposure in men). At a daily dose of 0.05 mg/kg/day (0.05-fold the expected clinical exposure), evidence of feminization was limited to a small, but statistically significant, decrease in anogenital distance. Doses of 2.5 to 30 mg/kg/day resulted in prolonged gestation in the parental females and a decrease in time to vaginal patency for female offspring and decrease prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were noted at doses greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day.

Feminization of male fetuses is an expected physiological consequence of inhibition of the conversion of testosterone to DHT by 5α-reductase inhibitors. These results are similar to observations in male infants with genetic 5α-reductase deficiency.

In the rabbit, embryo-fetal study doses of 30, 100, and 200 mg/kg (28- to 93-fold the expected clinical exposure in men) were administered orally on days 7 to 29 of pregnancy to encompass the late period of external genitalia development. Histological evaluation of the genital papilla of fetuses revealed evidence of feminization of the male fetus at all doses. A second embryo-fetal study in rabbits at doses of 0.05, 0.4, 3.0, and 30 mg/kg/day (0.3- to 53-fold the expected clinical exposure) also produced evidence of feminization of the genitalia in male fetuses at all doses. It is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

Nursing Mothers: TRADENAME is not indicated for use in women. It is not known whether dutasteride is excreted in human milk.

Pediatric Use: TRADENAME is not indicated for use in the pediatric population. Safety and effectiveness in the pediatric population have not been established.

Geriatric Use: Of 2166 male subjects treated with TRADENAME in three clinical studies, 60% were 65 and over and 15% were 75 and over. No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS:

Adverse reactions were generally mild and transient. The most common adverse events leading to withdrawal in both treatment groups were associated with the reproductive system.

The data described below reflect exposure to TRADENAME in 2166 male subjects, including 1772 exposed for one year. Over 4300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg daily doses of TRADENAME in three identical, placebo-controlled Phase III treatment

studies. The population was aged 47 to 94 years (mean age 66 years) and greater than 90% Caucasian. A total of 267 subjects (6% of each treatment group) were withdrawn from the studies due to adverse experiences, usually associated with the reproductive system. Withdrawals due to adverse events considered by the investigator to have a reasonable possibility of being caused by the study medication occurred in 3% of the subjects receiving TRADENAME and in 2% of the subjects receiving placebo. Table 1 summarizes clinical adverse reactions that were reported by the investigator as drug-related in at least 1% of subjects receiving TRADENAME and at a higher incidence than subjects receiving placebo.

Table 1: Drug-related Adverse Events* Reported in ≥1% Subjects and More Frequently in the TRADENAME Group than the Placebo Group

Pivotal Studies Pooled

Adverse Event	**Placebo** (N = 2158)	**TRADENAME** (N = 2166)
Impotence	59 (3%)	117 (5%)
Decreased libido	40 (2%)	74 (3%)
Ejaculation disorders	14 (<1%)	40 (2%)
Gynecomastia†	10 (<1%)	29 (1%)

*** A drug-related adverse event is one considered by the investigator to have a reasonable possibility of being caused by the study medication. In assessing causality, investigators were asked to select from one of two options: reasonably related to study medication or unrelated to study medication.**

†Includes breast tenderness and breast enlargement

Long-Term Treatment: The incidence of sexual adverse events considered by the investigator to have a reasonable possibility of being drug-related decreased with duration of treatment; after the first 6 months of treatment the incidence of onset of impotence, decreased libido, ejaculation disorders or gynecomastia was <1% for subjects receiving either TRADENAME or placebo.

The adverse event profile for 677 subjects who were maintained on TRADENAME 0.5 mg/day for 24 months in one pivotal study was consistent with that observed after 12 months of treatment in the three studies combined. The incidence of onset of drug-related events was lower during the second

year of treatment compared with the first year of treatment, with the exception of gynecomastia (onset in 1% during first year and 2% during second year).

OVERDOSAGE: In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without adverse events or significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride into consideration.

DOSAGE AND ADMINISTRATION: The recommended dose of TRADENAME is 1 capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole. TRADENAME may be administered with or without food.

No dosage adjustment is necessary for subjects with renal impairment or for the elderly (see **CLINICAL PHARMACOLOGY**: Pharmacokinetics: Geriatric and Renal Impairment). Due to the absence of data in patients with hepatic impairment, no dosage recommendation can be made (see PRECAUTIONS: General).

HOW SUPPLIED: TRADENAME Soft Gelatin Capsules 0.5 mg are oblong, opaque, dull yellow, gelatin capsules imprinted with "GX CE2" in red ink on one side packaged in bottles of 100 (NDC 0173-0712-00) with child-resistant closures and unit dose blister packs of 70 capsules (NDC 0173-0712-01).

Storage and Handling: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dutasteride is absorbed through the skin. TRADENAME Soft Gelatin capsules should not be handled by women who are pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus (see CLINICAL PHARMACOLOGY: Pharmacokinetics, WARNINGS: Exposure of Women—Risk to Male Fetus, and PRECAUTIONS: Information For Patients and Pregnancy).

Manufactured by:

RP Scherer

Beinheim, France for

GlaxoSmithKline

Research Triangle Park, NC 27709

(Date of Issue) RL-XXX

Patient Information

TRADENAME (dutasteride) Soft Gelatin Capsules

TRADENAME is for use by men only.

Read this information carefully before you start taking TRADENAME. Read the information you get with TRADENAME each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

What is TRADENAME?

TRADENAME is a medication to treat men who have symptoms of benign prostatic hyperplasia.

TRADENAME is not a treatment for prostate cancer. See the end of this leaflet for information about how TRADENAME works.

Who should NOT take TRADENAME?

- Women and children should not take TRADENAME. A woman who is pregnant or capable of becoming pregnant should not handle TRADENAME capsules. See **"What are the special warnings for women about TRADENAME?"**
- Do not take TRADENAME if you have had an allergic reaction to TRADENAME or any of its ingredients.
- Tell your doctor if you have liver problems. TRADENAME may not be right for you.

What are the special warnings for women about TRADENAME?

- Women should never take TRADENAME.
- Women who are pregnant or may become pregnant should not handle TRADENAME Capsules. If a woman who is pregnant with a male baby gets enough TRADENAME into her body after

swallowing it or through her skin after handling it, the male baby may be born with abnormal sex organs.

What are the special precautions about TRADENAME?

- Men treated with TRADENAME should not donate blood until at least 6 months after their final dose to prevent giving TRADENAME to a pregnant female through a blood transfusion.

How should I take TRADENAME?

- Take 1 TRADENAME capsule once a day.
- Swallow the capsule whole.
- You can take TRADENAME with or without food.
- If you miss a dose, you may take it later that day. Do not make up the missed dose by taking 2 doses the next day.
- You may find it helpful to take TRADENAME at the same time every day to help you remember to take your dose.

What are the possible side effects of TRADENAME?

The most common side effects of TRADENAME are impotence (trouble getting or keeping an erection), a decrease in libido (sex drive), and enlarged breasts. Also, some men may notice a decrease in the amount of semen they release during sex.

Talk with your doctor if you have questions about these and other side effects that you think may be related to taking TRADENAME.

How should I store TRADENAME?

TRADENAME is a soft gelatin capsule that may become soft and leak or may stick to other capsules if kept at high temperatures. Store TRADENAME capsules at room temperature of 77°F (25°C) or lower.

If your capsules are cracked or leaking, don't use them, and contact your pharmacist.

General information about TRADENAME.

- Do not use TRADENAME for a condition for which it was not prescribed.
- Do not share your TRADENAME.
- Ask your doctor about how often you should return for a visit to check your BPH.
- A blood test called PSA (prostate-specific antigen) is sometimes used to detect prostate cancer. TRADENAME will reduce the amount of PSA measured in your blood. Your doctor is aware of this effect and can still use PSA to detect prostate cancer in you.
- If you have questions about TRADENAME, ask your doctor or pharmacist. They can show you detailed information about TRADENAME that was written for healthcare professionals.

How does TRADENAME work?

Prostate growth is caused by a hormone in the blood called dihydrotestosterone (DHT). TRADENAME lowers DHT production in the body, leading to shrinkage of the enlarged prostate in most men. Just as your prostate became large over a long period of time, reducing the size of your prostate and improving your symptoms will take time. While some men have fewer problems and symptoms after 3 months of treatment with TRADENAME, a treatment period of at least 6 months is usually necessary to see if TRADENAME will work for you.

Manufactured by:
RP Scherer
Beinheim, France for

GlaxoSmithKline
Research Triangle Park, NC 27709

(Date of Issue) RL-XXX

EXHIBIT 5

United States Patent No. 5,565,467

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United States Patent [19]

Batchelor et al.

[11] Patent Number: 5,565,467

[45] Date of Patent: Oct. 15, 1996

[54] ANDROSTENONE DERIVATIVE

[75] Inventors: Kenneth W. Batchelor, Chapel Hill; Stephen V. Frye, Durham; George F. Dorsey, Jr., Raleigh; Robert A. Mook, Jr., Chapel Hill, all of N.C.

[73] Assignee: Glaxo Wellcome Inc., Research Triangle Park, N.C.

[21] Appl. No.: 405,120

[22] Filed: Mar. 16, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 123,280, Sep. 17, 1993, abandoned.

[51] Int. Cl.[6] A61K 31/58

[52] U.S. Cl. 514/284; 546/77

[58] Field of Search 514/284; 546/77

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Primary Examiner—Donald G. Daus

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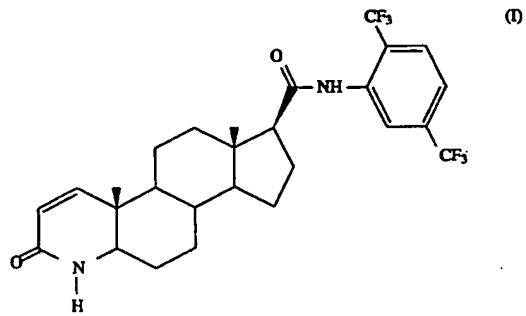
[57] ABSTRACT

The present invention relates to the compound of formula (I),



(I)

also known as 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one, solvates thereof, its preparation, intermediates used in its preparation, pharmaceutical formulations thereof and its use in the treatment of androgen responsive and mediated diseases.

10 Claims, No Drawings

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ANDROSTENONE DERIVATIVE

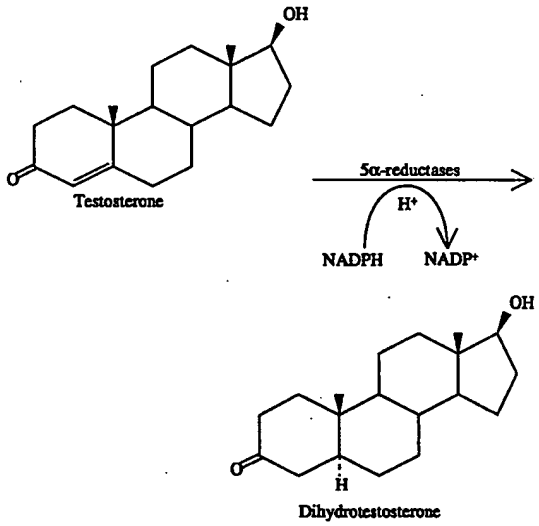
This patent application is a continuation-in-part of PCT application No. pending PCT/US94/10530, filed Sep. 16, 1994 in the name of Glaxo Inc which is a continuation-in-part of U.S. Ser. No. 08/123,280 filed Sep. 17, 1993 and now abandoned.

The present invention relates to a particular 17β-anilide-4-aza-5α-androst-1-en- 3-one derivative, as a surprisingly potent and selective dual inhibitor of type 1 and 2 human 5α-reductase.

BACKGROUND OF THE INVENTION

Androgens are responsible for many physiological functions in both males and females. Androgen action is mediated by specific intracellular hormone receptors expressed in androgen responsive cells. Testosterone, the major circulating androgen, is secreted by Leydig cells of the testes under the stimulation of pituitary-derived luteinizing hormone (LH). However, reduction of the 4, 5 double bond of testosterone to dihydrotestosterone (DHT) is required in some target tissues, such as prostate and skin, for androgen action. Steroid 5α-reductases in target tissues catalyze conversion of testosterone to DHT in an NADPH dependent fashion as shown in Scheme A.

SCHEME A

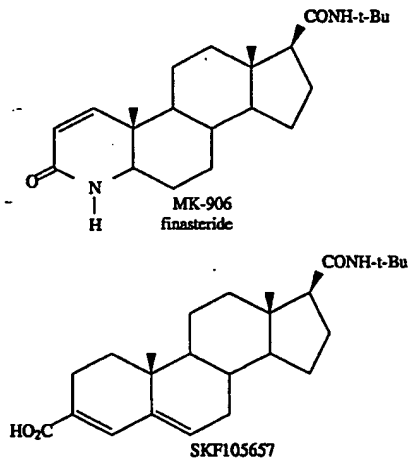


The requirement for DHT to act as an agonist in these target tissues has been highlighted by studies of steroid 5α-reductase deficient individuals who have vestigial prostate glands and do not suffer from acne vulgaris or male pattern baldness (see McGinley, J. et al., *The New England J. of Medicine*, 300, 1233 (1979)). Thus, inhibition of the conversion of testosterone to DHT in these target tissues is anticipated to be useful in the treatment of a variety of androgen responsive diseases, e.g., benign prostatic hyperplasia, prostate cancer, acne, male pattern baldness and hirsutism.

Additionally, it has recently been discovered that two isozymes of 5α-reductase exist in humans which differ in their tissue distribution, affinity for testosterone, pH profile and sensitivity to inhibitors (see Russell, D. W. et al., *J. Clin. Invest.*, 89, 293 (1992); Russell, D. W. et al., *Nature*, 354, 159 (1991)). The steroid 5α-reductase deficient individuals studied by Imperato-McGinley are deficient in the type 2, 5α-reductase enzyme (Russell, D. W. et al., *J. Clin. Invest.*, 90, 799 (1992); Russell, D. W. et al., *New England J. Med.*, 327, 1216 (1992)), which is the predominant isozyme present in the prostate, while the type 1 isozyme is predominant in the skin. The relative value of isozyme specific and dual inhibitors of the two isozymes of 5α-reductase will depend upon the type of disease treated (benign prostatic hyperplasia, prostate cancer, acne, male pattern baldness or hirsutism) as well as the stage of the disease (prevention versus treatment) and the anticipated side-effects in the intended patients (for example treatment of acne vulgaris in pubescent males).

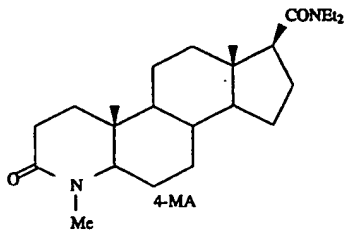
Because of their valuable therapeutic potential, testosterone 5α-reductase inhibitors [hereinafter "5α-reductase inhibitors"] have been the subject of active research worldwide. For example, see: Hsia, S. and Voight, W., *J. Invest. Derm.*, 62, 224 (1973); Robaire, B. et al., *J. Steroid Biochem.*, 8, 307 (1977); Petrow, V. et al., *Steroids*, 38, 121 (1981); Liang, T. et al., *J. Steroid Biochem.*, 19, 385 (1983); Holt, D. et al., *J. Med. Chem.*, 33, 937 (1990); U.S. Pat. No. 4,377,584, U.S. Pat. No. 4,760,071 and U.S. Pat. No. 5,017,568. Two particularly promising 5α-reductase inhibitors are MK-906 (Merck), known by the generic name, finasteride, and marketed under the trademark, Proscar; and SKF-105657 (SmithKline Beecham), shown in Scheme B.

SCHEME B



The potent inhibition of bovine adrenal and porcine granulosa cell 3β-hydroxy-Δ^5-steroid dehydrogenase / 3-keto-Δ^5-steroid isomerase (3BHSD) by the 4-azasteroid derivative, 4-MA, shown in Scheme C and not by the drug finasteride

SCHEME C

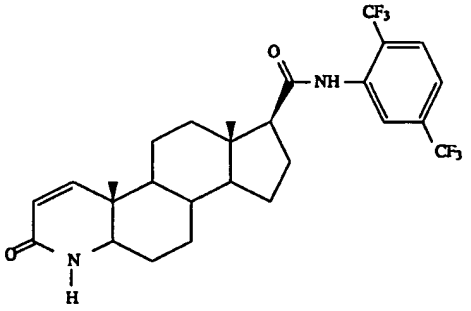


(Tan, C. H.; Fong, C. Y.; Chan, W. K. *Biochem. Biophys. Res. Comm.*, 144, 166 (1987) and Brandt, M.; Levy, M. A. *Biochemistry*, 28, 140 (1989)), along with the critical role of 3BHSD in steroid biosynthesis (Potts, G. O. et al., *Steroids*,

32, 257 (1978)), suggests that optimal inhibitors of type 1 and 2, 5α-reductase should also be selective versus human adrenal 3BHSD. The importance of selectivity in 5α-reductase inhibitors has been emphasized by reports of hepatotoxicity in certain 4-azasteroids such as 4-MA (McConnell, J. D. *The Prostate Suppl.*, 3, 49 (1990) and Rasmusson, G. H. et al. *J. Med. Chem.*, 27, 1690 (1984)).

SUMMARY OF THE INVENTION

One aspect of the present invention is the compound of formula (I),



(I)

also known as 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst- 1-en-3-one and pharmaceutically acceptable salts and solvates thereof.

Other aspects of the invention are:

1. A method of inhibiting testosterone-5α-reductases comprising contacting testosterone-5α-reductases with the compound of formula (I).
2. A method of treatment of androgen responsive or mediated disease comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment.
3. Pharmaceutical formulations containing the compound of formula (I) as an active ingredient.
4. A method of treatment of androgen responsive or mediated disease comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment in combination with an anti-androgen such as flutamide.
5. A method of treatment of benign prostatic hyperplasia comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment in combination with an alpha 1 adrenergic receptor blocker (e.g. terazosin).
6. A method of treatment of benign prostatic hyperplasia comprising administering an effective amount of the compound of formula (I) to a patient in need of such treatment in combination with an anti-estrogen.
7. Intermediates produced in during the synthesis of the compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

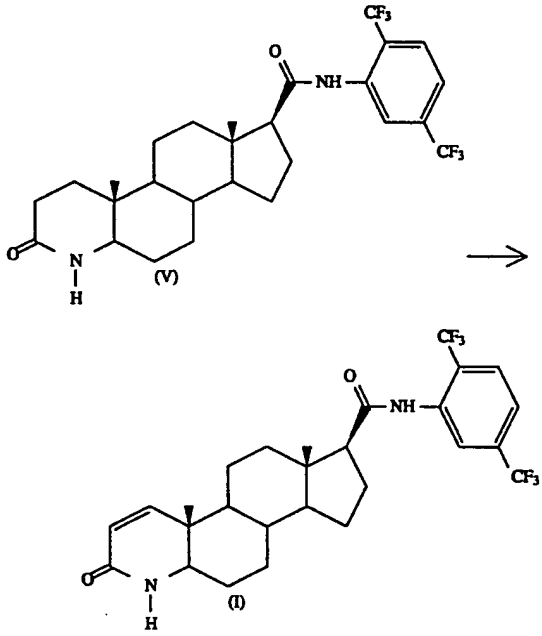
Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of compound (I) are within the scope of the invention.

It will also be appreciated by those skilled in organic chemistry that many organic compounds can exist in more than one crystalline form. For example, crystalline form may vary from solvate to solvate. Thus, all crystalline forms of the compounds of formula (I) or the pharmaceutically acceptable solvates thereof are within the scope of the present invention.

Preparation of Compounds

The compound of the present invention may be prepared by the methods taught in U.S. Pat. No. 4,377,584 (hereinafter, "'584") and U.S. Pat. No. 4,760,071 (hereinafter, "'071") both incorporated herein by reference. For example, the compound of formula (I) may be prepared by the procedure shown in Scheme I and II.

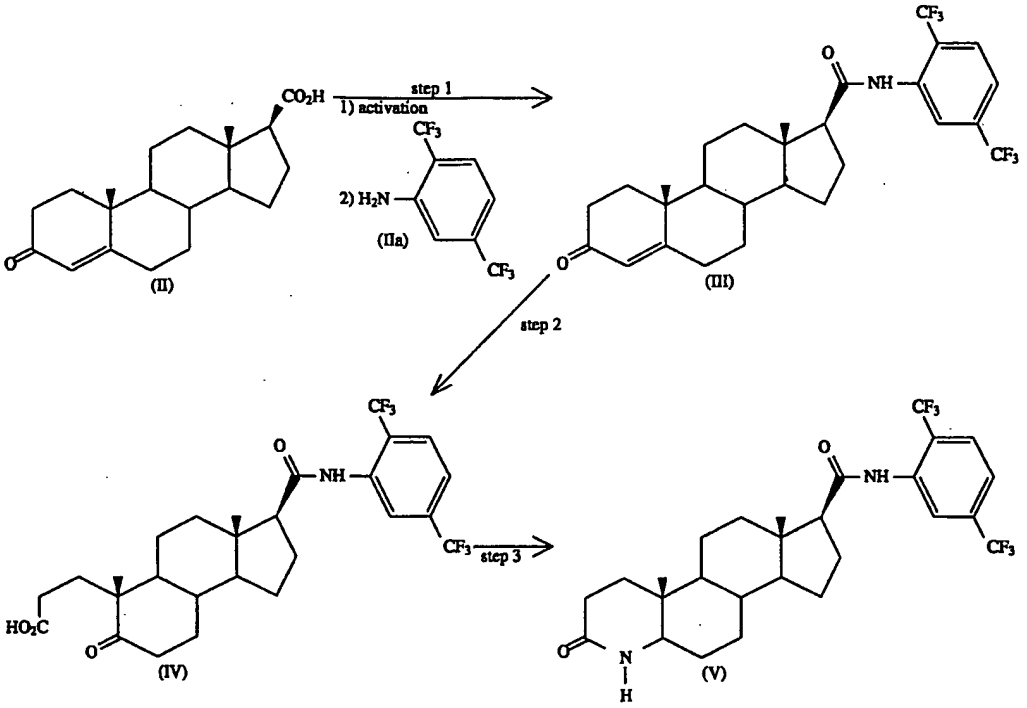
SCHEME I



In Scheme I, the compound of formula (V) is dehydrogenated to give the compound of formula (I) by treatment with a dehydrogenating system, e.g. 2,3-dichloro- 5,6-dicyano-1,4-benzoquinone (DDQ) and bis(trimethylsilyl)trifluoroacet-amide in dry dioxane at room temperature for 2–5 hrs followed by heating at reflux for 10–20 hrs (see Bhattacharya, A. et al., *J. Am. Chem. Soc.*, 110, 3318 (1988)).

The compound of formula (V) may be prepared according to Scheme IA

SCHEME IA

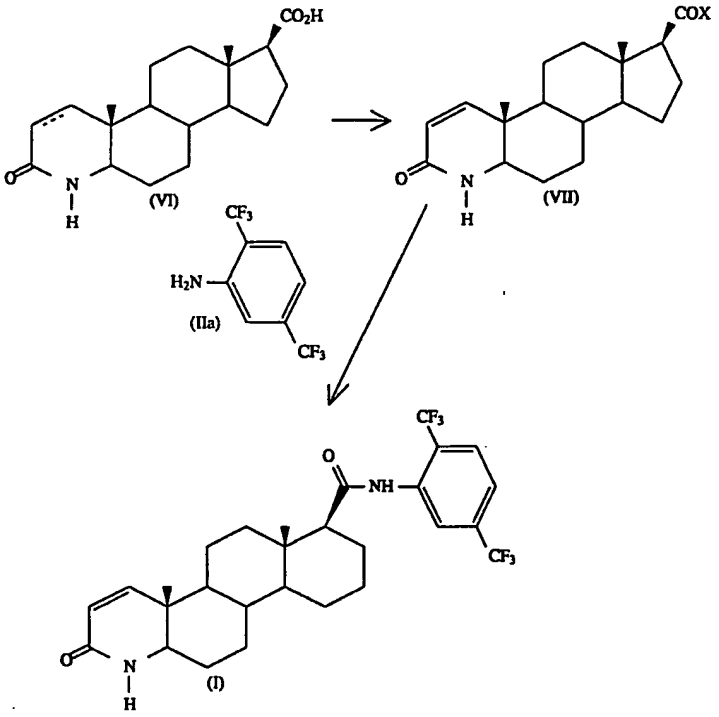


In Step 1 of Scheme IA, 3-oxo-4-androstene-17β-carboxylic acid, (II) is converted to the corresponding amide of formula (III). This may be accomplished by activation of the acid and reaction with an aniline of formula (IIa). For example, the reaction sequence can be the conversion of a compound of formula (II) to the corresponding acid halide by treatment with a halogenating agent such as thionyl chloride or oxalyl chloride in an aprotic solvent such as toluene or methylene chloride at −5° to 10° C. in the presence of a base such as pyridine.

The intermediate acid halide may be reacted with a substituted aniline of formula (IIa) at 25° to 100° C. in an aprotic solvent such as toluene or methylene chloride to give the amide of formula (III). The compound of formula (IIa) is commercially available (Aldrich Chemical Company, Milwaukee, Wis. 53201). In Step 2, the compound of formula (III) is converted to the 5-oxo-A-nor-3,5-secoandrostan- 3-oic acid derivative of formula (IV) by oxidation, e.g. by treatment with aqueous sodium permanganate and sodium periodate under basic conditions at reflux in t-butanol.

In Step 3, the compound of formula (IV) is converted to the 4-aza-5α-androstan- 3-one of formula (V) by treatment with ammonia at reflux in ethylene glycol followed by hydrogenation of the intermediate 4-aza-androst-5-en-3-one in acetic acid at 60° to 70° C. and 40–60 psi hydrogen pressure in the presence of catalytic platinum oxide.

SCHEME II



Alternatively, in Scheme II, the compound of formula (I) may be prepared from the 3-oxo-4-aza-5α-androst-1-en-17β-carboxylic acid of formula (VI) (Rasmusson, G. H. et al., *J. Med. Chem.*, 29, 2298 (1986)), through the acid halide intermediate of formula (VII), wherein X is halogen, particularly chloro. The acid chloride of formula (VII) may be produced by treating the corresponding acid of formula (VI) with thionyl chloride in solvents such as toluene, heptane, acetonitrile, triethylphosphate, ethyl acetate, dimethylformamide, N-methylpyrrolidinone, dimethylimidazolidinone and dimethyltetrahydropyrimidinone. Persons skilled in the art will realize the addition of a catalytic amount of dimethylformamide can be utilized for acid chloride formation.

The intermediate of formula (VII) wherein X is halogen may be reacted with a substituted aniline of formula (IIa), commercially available (Aldrich Chemical Company, Milwaukee, Wis. 53201, at 25° to 100° C. in an aprotic solvent such as toluene, heptane, acetonitrile, triethylphosphate, ethyl acetate, dimethylformamide, N-methylpyrrolidinone, dimethylimidazolidinone and dimethyltetrahydropyrimidinone to give the compound of formula (I). Bases such as dimethylaminopyridine to assist in the coupling can also be used. Alternative bases such as Diisopropylethylamine, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene might also be used in the preparation of the compound of formula (I). Persons skilled in the art will also realize that the addition of salts such as, LiCl and LiBr, might also be used to facilitate the coupling of the aniline of formula (IIa) with the acid halide of formula (VII) to produce the compound of formula (I).

Those skilled in the art will appreciate that at an earlier stage in the preparation of the compound of formula (I) or a solvate thereof it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of the compound of formula (I) may be used in a conventional manner. See for example Protective Groups in Organic Chemistry, Ed. J. F. W. McOmie, Plenum Press, London (1973) or Protective Groups in Organic Synthesis, Theodora Green, John Wiley and Sons, New York (1981).

Removal of any protecting groups present may be achieved by conventional procedures. An arylalkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst, e.g., palladium on charcoal; an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation.

As will be appreciated, in any of the general processes described above it may be desirable or even necessary to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes.

Thus, according to a further aspect of the invention, the following reactions may, if necessary and/or desired be carried out in any appropriate sequence subsequent to any of the general processes:

(i) removal of any protecting groups; and

(ii) conversion of a compound of formula (I) or a solvate thereof into a pharmaceutically acceptable solvate thereof.

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such

multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The compound of formula (I) and the intermediate compounds, (II)–(VI), shown in Schemes I and II may be purified by convenient methods of the art, e.g., chromatography or crystallization.

IN VITRO ASSAYS

Steroid 5α-Reductases

Enzyme activies may be determined using microsomes derived from: 1) prostate tissue from benign prostatic hyperplasia (BPH) patients; 2) recombinant baculovirus infected SF9 cells that express human type 1 5α-reductase; or 3) recombinant baculovirus infected SF9 cells that express human type 2 5α-reductase. Microsomes were prepared by homogenization of the tissue or cells, followed by differential centrifugation of the homogenate. Microsome extracts were incubated with varying concentrations of [1,2,6,7-3H] -testosterone, 1 mM NADPH, and varying amounts of the compounds of Formula I, i.e. a test compound, in buffer containing a NADPH regenerating system capable of maintaining NADPH concentrations for a period of time within the range 0.5–240 minutes. Corresponding incubations were carried out with no test compound as a control study. For clone 1 IC_{50} measurements, assay components except testosterone were preincubated for 10 minutes at pH 7.0, and following the addition of 100 nM testosterone the assays were allowed to proceed for 10–120 minutes. For clone 2 IC_{50} measurements, assay components except testosterone were preincubated for 20 minutes at pH 6.0, and following the addition of 8 nM testosterone the assays were allowed to proceed for 20–40 minutes. The percentage of conversion of testosterone to DHT in the presence of test compounds compared to the corresponding conversion in the control study was estimated using high pressure liquid chromatography (HPLC) with radiochemical detection. The results of these assays appear as IC_{50}'s reported in Table 1.

3β-Hydroxy-Δ^5-steroid Dehydrogenase / 3-Keto-Δ^5-Steroid Isomerase

Enzyme activities are measured using microsomes derived from human adrenal tissues. Microsomes were prepared by homogenization of the tissue followed by differential centrifugation of the homogenate. Microsome extracts were incubated with varying concentrations of dehydroepiandrosterone (DHEA), 1 mM NAD+, and varying amounts of the compound of Formula (I), i.e. a test compound, in pH 7.5 buffer for a period of time within the range of 1 to 60 minutes. Corresponding incubations were carried out with no test compound as a control study. The percentage of conversion of DHEA to androstenedione in the presence of test compounds compared to the corresponding conversion in the control study was estimated using HPLC with radiochemical detection. The results of these assays appear as K_i's reported in Table 1.

TABLE 1

5α-Reductase (5αR) and Human Adrenal 3β-Hydroxy-Δ^5-Steroid Dehydrogenase/3-Keto-Δ^5-Steroid Isomerase (3βHSD) In Vitro Inhibitory Activity

IC_{50} Human Type 1 5AR	IC_{50} Human Type 2 5AR	K_i Human Adrenal 3BHSD
<1 nM	<1 nM	>1000 nM

In vivo Evaluation of Steroid 5α-Reductase Inhibitors

The in vivo activity of steroid 5α-reductase inhibitors may be determined in a chronic rat model (Brooks, J. R. et al., *Steroids*, 47, 1 (1986)). The chronic model utilizes castrated male rats that are dosed daily with testosterone (20 μg/rat) subcutaneously and with test compound (0.01–10 mg/kg) or vehicle orally for 7 days. The animals are then sacrificed and their prostates weighed. Reduction in the size of testosterone-stimulated prostate weight demonstrated activity of the test compound. Known steroid 5α-reductase inhibitors were tested in parallel to ensure consistency of the assay method.

Utility

The steroid 5α-reductase inhibitor of the present invention is useful in the treatment of androgen responsive diseases, e.g., benign and malignant diseases of the prostate, especially benign prostatic hyperplasia, in a manner similar to that for other 5α-reductase inhibitors such as finasteride and SKF105657. However, the compound of the present invention has a surprisingly long half-life and potency compared to finasteride and SKF105657. For correlation of in vitro, rat in vivo and human clinical data relating to an inhibitor of 5α-reductase, see Stoner, E. et al., *J. Steroid Biochem. Molec. Biol.*, 37, 375 (1990); Brooks, J. R. et al., *Steroids*, 47, 1 (1986) and Rasmusson, G. H. et al., *J. Med. Chem.*, 29, 2298 (1986)).

The compound of this invention is also useful in the treatment of prostatitis, prostate cancer, androgen mediated diseases of the skin, such as acne, hirsutism and male pattern baldness. Other hormone related diseases, e.g., polycystic ovary disease, may also be treated with this compound.

The amount of the compound of formula (I) required to be effective as an 5α-reductase inhibitor will, of course, vary with the individual mammal being treated and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, the nature of the formulation, the mammal's body weight, and surface area, age and general condition of the mammal. However, for a human patient a suitable effective 5α-reductase inhibitory dose is in the range of about 0.001 to about 2 mg/kg body weight per day, preferably in the range of about 0.005 to about 1 mg/kg per day.

The total daily dose may be given as a single dose, multiple doses, e.g., two to six times per day, or by intravenous infusion for a selected duration. Dosages above or below the range cited above are within the scope of the present invention and may be administered to the individual patient if desired and necessary. For example, for a 75 kg mammal, a dose range would be about 0.04 mg to about 75 mg per day, and a typical dose would be about 10 mg per day. Because of the long half-life of the compound of the present invention, for many patients treatment may only be required every other day, even every third day and possibly less often. If discrete multiple doses are indicated, treatment might typically be 2.5 mg of a compound of formula (I) given 4 times per day.

Formulations

Formulations of the present invention for medical use comprise an active compound, i.e., the compound of formula (I), together with an acceptable carrier thereof and optionally

other therapeutically active ingredients. The carrier must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention, therefore, further provides a pharmaceutical formulation comprising a compound of formula (I) together with a pharmaceutically acceptable carrier thereof.

The formulations include those suitable for oral, topical, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration. Preferred are those suitable for oral or parenteral administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier and then, if necessary, shaping the product into desired unit dosage form.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension or solution in an aqueous liquid or non-aqueous liquid, e.g., a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form, e.g., a powder or granules, optionally mixed with accessory ingredients, e.g., binders, lubricants, inert diluents, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup or suspension may be made by adding the active compound to a concentrated, aqueous solution of a sugar, e.g., sucrose, to which may also be added any accessory ingredients. Such accessory ingredient(s) may include flavoring, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, e.g., as a polyhydric alcohol, for example, glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a conventional carrier, e.g., cocoa butter or Witepsol S55 (trademark of Dynamite Nobel Chemical, Germany), for a suppository base.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in distilled water or saline and the compound of the formula (I) that has an appropriate solubility in these solvents. Useful formulations also comprise concentrated solutions or solids containing the compound of formula (I) which upon dilution with an appropriate solvent give a solution suitable for parenteral administration above.

Topical formulations include ointments, creams, gels and lotions which may be prepared by conventional methods known in the art of pharmacy. In addition to the ointment, cream gel, or lotion base and the active ingredient, such topical formulation may also contain preservatives, perfumes, and additional active pharmaceutical agents.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more optional accessory ingredient(s) utilized in the art of pharmaceutical formulations, e.g., diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, suspending agents, preservatives (including antioxidants) and the like.

EXAMPLES

The following examples illustrate aspects of this invention but should not be construed as limitations. The symbols and conventions used in these examples are consistent with those used in the contemporary chemical literature, for example, the *Journal of the American Chemical Society.* As used here in the term "room temperature" means about 25° C.

EXAMPLE 1

17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one

Synthesis of Scheme I

A. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-androst-4-en-3-one

To a solution of 3-oxo-4-androstene-17β-carboxylic acid (Rasmusson, G. H. et al., *J. Med. Chem.*, 27, 1690 (1984)) (17.2 g, 54.4 mmol), dry THF (180 mL) and dry pyridine (7 ml) at 2° C. is added thionyl chloride (5.1 mL, 70.8 mmol). The reaction mixture is stirred at 2° C. for 20 min and then stirred at room temperature for 40 min. The reaction mixture is then filtered and the solid washed with toluene. The filtrate is concentrated in vacuo to an oil which is diluted with dry THF (150 mL) and dry pyridine (7 mL). To the resultant dark solution is added 2,5-bis-(trifluoromethyl)aniline (9.4 mL, 59.8 mmol) and the reaction mixture is refluxed for 5 h, diluted with methylene chloride, extracted sequentially with 1N HCl and brine, dried over sodium sulfate, and filtered. The filtrate is concentrated and applied to a column of 500 g of silica gel and the column eluted with a 15–30% ethyl acetate-hexane gradient to give, after concentration, 17β-N-(2,5-bis(trifluoromethyl))phenyl-carbamoyl-androst-4-en-3-one as an off-white foam.

B. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-5-oxo-A-nor-3,5-secoandrostan- 3-oic acid

To a refluxing solution of 17βN-(2,5-bis(trifluoromethyl))phenylcarbamoyl-androst- 4-en-3-one (18.3 g, 34.9 mmol) prepared as in part A above, t-butanol (275 mL), sodium carbonate (6.3 g, 50.8 mmol), and water (36 mL) is added, over 45 min, a 75° C. solution of potassium permanganate (0.38 g, 2.4 mmol), sodium periodate (52.2 g, 245 mmol) and water (311 mL). After refuxing an additional 15 min, the heterogeneous mixture is cooled to room temperature and celite (50 g) is added. The reaction mixture is filtered through a bed of celite (50 g) and the solid is washed with water and the filtrate concentrated in vacuo to remove t-butanol (ca. 175 ml). The resultant aqueous solution is acidified to pH 2 with 36% HCl and the extracted 4 times with chloroform. The chloroform layers are combined and washed with water, brine, dried over sodium sulfate, filtered and concentrated in vacuo to give 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl- 5-oxo-A-nor-3,5-secoandrostan-3-oic acid as a off-white solid. This material is carried directly into step C below.

C. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-androst-5-en-3-one

To a suspension of 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-5-oxo-A-nor- 3,5-secoandrostan-3-oic acid (20.5 g, 34.8 mmol), as prepared in step B, in dry ethylene glycol (100 mL) at room temperature is added ammonia (ca. 8 mL, 0.32 mol) over a 5 min period. The resultant solution is heated to 180° C. over 45 min, and after 12 min at 180° C., the reaction mixture is cooled to 70° C. and water (116 mL) is added over a period of 5 min. The resultant suspension is cooled to 7° C. and stirred for 10 min and filtered under vacuum. The solid is washed with water (60 mL) and then is dissolved in chloroform and washed with water, brine, dried over sodium sulfate, filtered and concentrated. The residue is dissolved in chloroform and applied to a column of 110 g of silica gel and the column eluted with a 2–5% isopropanol-chloroform gradient to give 17β-N-(2,5-bis(trifluoromethyl))phenyl-carbamoyl- 4-aza-androst-5-en-3-one as an off-white solid.

D. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androstan-3-one

To a solution of 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl-4-aza-androst- 5-en-3-one (8.9g, 16.7 mmol) in acetic acid (120 mL) is added platinum oxide (0.9 g). The resultant mixture is charged to 50 psi with hydrogen and heated at 60°–70° C. for 6 h. After replacing the hydrogen atmosphere with nitrogen, the reaction mixture is filtered through celite and the celite pad washed with acetic acid (30 mL), chloroform (60 mL) and toluene (200 mL). The filtrate is concentrated in vacuo to an oil, toluene (200 mL) is added and the solution concentrated to a foam in vacuo. The foam is crystallized from ethyl acetate-heptane to give, after drying in vacuo at 85° C. for 1 h, 17β-N-(2,5-bis(trifluoromethyl))phenylcarbamoyl- 4-aza-5α-androstan-3-one; m.p. 245°–247° C.

Anal. Calcd. for $C_{27}H_{32}F_6N_2O_2$: C, 61.12; H, 6.08; N, 5.28. Found: C, 61.13; H, 6.12; N, 5.21.

E. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androstan-1-en-3-one

To a suspension of 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza- 5α-androstan-3-one (7.24 g, 13.7 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.41 g, 15 mmol) in dry dioxane (168 mL) at room temperature is added bis(trimethylsilyl)trifluoroacetamide (14.5 mL, 54.6 mmol). After stirring at room temperature for 7 h, the reaction mixture is refluxed for 18 h. The resultant dark solution is cooled to room temperature and is concentrated in vacuo to a dark oil. Methylene chloride (100 mL) and a 1% sodium bisulfite solution (40 mL) is added to the oil and the two phase mixture is stirred rapidly for 15 min and filtered. The two filtrate layers are separated and the methylene chloride layer is washed sequentially with 2N HCl and brine, dried over sodium sulfate, filtered, and concentrated to a brown oil. The oil is diluted with toluene and is applied to a column of 300 g of silica gel and eluted with a 12:3:1 to 9:3:1 gradient of toluene:acetone:ethyl acetate to give 17β-N-(2,5-bis(trifluoromethyl))phenyl-carbamoyl- 4-aza-5α-androst-1-en-3-one as a foam. This material is crystallized from ethyl acetate-heptane (1:1) to give a white solid; m.p. 244°–245° C. ^{13}C NMR (100 MHz, $CHCl_3$) d 171.31, 166.77, 151.04, 136.35 (q, J=1.4 Hz), 135.01 (q, J=33.1 Hz), 126.73 (q, J=5.4 Hz), 123.44 (q, J=273.5 Hz), 123.03 (q, J=273.2 Hz) 122.84, 121.58 (qq, J=30.4, 1.0 Hz), 120.37 (q, J=3.6 Hz), 120.29 (q, J=3.9 Hz), 59.58, 58.33, 55.69, 47.46, 44.78, 39.30, 37.81, 35.29, 29.34, 25.70, 24.17, 23.59, 21.15, 13.40, 11.91.

Anal. Calcd. for $C_{27}H_{30}F_6N_2O_2$: C, 61.36; H, 5.72; N, 5.30. Found: C, 61.36; H, 5.73; N, 5.23.

EXAMPLE 2

17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one

Synthesis of Scheme II

A solution of 3-oxo-4-aza-5a-androst-1-en-17β-carboxylic acid (31.7 g, 100 mmol) in pyridine (800 mL) is cooled to −10° C., and thionyl chloride (14.3 g, 120 mol) is added with stirring. The mixture is allowed to stir 2.5–3 hours at 20° C., to form the acid chloride (17β-chlorocarbonyl-4-aza-5α-androst-1-en-3-one); IR 1780 cm^{-1}, FAB-MS $[MH]^+$=336.

To the stirring acid chloride 2,5-bis(trifluoromethyl)aniline (23.1 g, 101 mol) is added. Stirring is continued for 4–6 hours, 960 mL of water is added and the slurry is stirred at room temperature overnight. Filtration gives the crude product as an off-white solid. The crude solid is recrystallized by dissolution in 725 mL of acetonitrile at 70° C. and removal of acetonitrile by distillation gives, after cooling and filtration, 17β-N-2,5-bis(Trifluoromethyl)phenylcarbamoyl-4-aza- 5α-androst-1-en-3-one as a white crystalline solid.

EXAMPLE 3

Pharmaceutical formulations

"Active compound" is the compound of Formula (I)

(A) Transdermal System - For 1000 Patches

Ingredients	Amount
Active compound	40 g
Silicone fluid	450 g
Colloidal silicon dioxide	25 g

The silicone fluid and active compound are mixed together and the colloidal silicone dioxide is added to increase viscosity. The material is then dosed into a subsequently heat sealed polymeric laminate comprised of the following: polyester release liner, skin contact adhesive composed of silicone or acrylic polymers, a control membrane which is a polyolefin (e.g. polyethylene, polyvinyl acetate or polyurethane), and an impermeable backing membrane made of a polyester multilaminate. The resulting laminated sheet is then cut into 10 sq. cm patches.

(B) Oral Tablet - For 1000 Tablets

Ingredients	Amount
Active compound	20 g
Starch	20 g
Magnesium Stearate	1 g

The active compound and the starch are granulated with water and dried. Magnesium stearate is added to the dried granules and the mixture is thoroughly blended. The blended mixture is compressed into tablets.

(C) Suppository - For 1000 Suppositories

Ingredients	Amount
Active compound	25 g
Theobromine sodium salicylate	250 g

-continued

(C) Suppository - For 1000 Suppositories

Ingredients	Amount
Witepsol S55	1725 g

The inactive ingredients are mixed and melted. The active compound is then distributed in the molten mixture, poured into molds and allowed to cool.

(D) Injection - For 1000 Ampules

Ingredients	Amount
Active Compound	5 g
Buffering Agents	q.s.
Propylene glycol	400 mg
Water for injection	600 mL

The active compound and buffering agents are dissolved in the propylene glycol at about 50° C. The water for injection is then added with stirring and the resulting solution is filtered, filled into ampules, sealed and sterilized by autoclaving.

(E) Capsule - For 1000 Capsules

Ingredients	Amount
Active Compound	20 g
Lactose	450 g
Magnesium stearate	5 g

The finely ground active compound is mixed with the lactose and stearate and packed into gelatin capsules.

What is claimed is:

1. 17β-N-(2,5-bis(Trifluoromethyl))phenylcarbamoyl-4-aza-5α-androst-1-en-3-one or a pharmaceutically acceptable solvate thereof.

2. A pharmaceutical formulation comprising the compound of claim 1 and a pharmaceutically acceptable carrier thereof.

3. A pharmaceutical formulation comprising a safe and effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier thereof.

4. The pharmaceutical formulation of claim 3 further comprising an alpha 1 adrenergic receptor blocker.

5. The pharmaceutical formulation of claim 4 wherein the alpha 1 adrenergic receptor blocker is selected from the group consisting of: prazosin, terazosin, doxazosin, indoramin, trimazosin and tamsolosin.

6. The pharmaceutical formulation of claim 5 wherein the alpha 1 adrenergic receptor blocker is terazosin.

7. The pharmaceutical formulation of claim 3 further comprising an anti-estrogen selected from the group consisting of: clomiphene and tamoxifen.

8. The pharmaceutical formulation of claim 7 wherein an the anti-estrogen is tamoxifen.

9. The pharmaceutical formulation of claim 3 further comprising an anti-androgen.

10. The pharmaceutical formulation of claim 9 wherein the anti-androgen is flutamide.

* * * * *

EXHIBIT 6

Petition to Correction Inventorship filed in United States

Patent Application No. 08/405,120

U.S. Patent No. 5,565,467

Express Mail Label No.:
EL395889738US

9200 GAU 1611

G1070USW

122

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,565,467

Date of Issue: ~~July 31~~ Oct. 15, 1996

Name of Patentee: Kenneth William BATCHELOR, et al.

Title of Invention: ANDROSTENONE DERIVATIVE

Assistant Commissioner for Patents
Washington, D.C. 20231

Attention: solicitor (M.P.E.P. § 1002.02(k))

PETITION FOR CORRECTION OF INVENTORSHIP OF PATENT
(37 C.F.R. § 1.324)

1. This is a petition for correction of error in a misjoinder of inventors in the above issued patent. It is respectfullly requested that the PTO issue a certificate correcting the error.

2. Enclosed herewith is (37 C.F.R. § 1.324(b)):

A. a statement from each person who is being deleted as an inventor that the inventorship error occurred without any deceptive intention on his or her part.

B. A statement from the current named inventors who have not submitted a statement under A. above:

- Agreeing to the change of inventorship
- Stating that there is no disagreement in regard to the requested change.

3. Also enclosed is the written concent of the assignee.

4. The fee required (37 C.F.R. § 1.20(b) is paid as follows:

Please charge Deposit Account No. 07-1392 in the amount of $130.00.

G1070USW

Please charge any shortage in the fees or credit any overpayment to deposit Account No. 02-1392 pursuant to 37 C.F. R. § 1.16 or 1.17.

Respectfully submitted,

GLAXO WELLCOME INC.

By: Robert H. Brink
Robert H. Brink
Registration No.36,094

Dated: May 17, 1999

Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, NC 27709
Telephone: (919) 483-3323
Facsimile: (919) 483-7988

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231 ON _____
IN ACCORDANCE WITH THE PROVISIONS OF 37 CFR 1.8.

_____
SIGNATURE

_____
PRINTED NAME

G1070USW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTEE: Kenneth William BATCHELOR, et al.

PATENT NO.: 5,565,467 ISSUED: July 31, 1996

TITLE: ANDROSTENONE DERIVATIVE

STATEMENT UNDER 37 CFR §1.48(a) OF NO DECEPTIVE INTENT IN FAILING TO NAME INVENTOR

Assistant Commissioner for Patents
Washington, D.D. 20231

Sir:

I, Robert a. Mook, Jr. do hereby declare and say as follows:

At the time of filing the application for the above patent, I was named as an inventor. However, the claims for which I was an inventor were deleted during prosecution and are not contained in the above patent. The error in inventorship of the instant patent application occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued therefrom.

Robert A. Mook, Jr.

5 May 99
Date

G1070USW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTEE: Kenneth William BATCHELOR, et al.

PATENT NO.: 5,565,467 ISSUED: July 31, 1996

TITLE: ANDROSTENONE DERIVATIVE

STATEMENT UNDER 37 CFR §1.48(a) OF NO DECEPTIVE INTENT IN FAILING TO NAME INVENTOR

Assistant Commissioner for Patents
Washington, D.D. 20231

Sir:

I, George F. Dorsey, Jr., do hereby declare and say as follows:

At the time of filing the application for the above patent, I was named as an inventor. However, the claims for which I was an inventor were deleted during prosecution and are not contained in the above patent. The error in inventorship of the instant patent application occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued therefrom.

George F. Dorsey, Jr.

5/7/1999
Date

G1070USW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTEE: Kenneth William BATCHELOR, et al.

PATENT NO.: 5,565,467 ISSUED: July 31, 1996

TITLE: ANDROSTENONE DERIVATIVE

STATEMENT UNDER 37 CFR §1.48(a) OF NO DECEPTIVE INTENT IN FAILING TO NAME INVENTOR

Assistant Commissioner for Patents
Washington, D.D. 20231

Sir:

I, Kenneth W. Batchelor, do hereby declare and say as follows:

At the time of filing the application for the above patent, I was named as an inventor. I agree with the requested change in inventorship to delete George F. Dorsey, Jr. and Robert A. Mook, Jr. from the above patent. The error in inventorship of the instant patent application occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued therefrom.

Kenneth W Batchelor
Kenneth W. Batchelor

9th May 1999
Date

G1070UsW

THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENTEE: Kenneth William BATCHELOR, et al.

PATENT NO.: 5,565,467 ISSUED: July 31, 1996

TITLE: ANDROSTENONE DERIVATIVE

STATEMENT UNDER 37 CFR §1.48(a) OF NO DECEPTIVE INTENT IN FAILING TO NAME INVENTOR

Assistant Commissioner for Patents
Washington, D.D. 20231

Sir:

I, Stephen V. Frye, do hereby declare and say as follows:

At the time of filing the application for the above patent, I was named as an inventor. I agree with the requested change in inventorship to delete George F. Dorsey, Jr. and Robert A. Mook, Jr. from the above patent. The error in inventorship of the instant patent application occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued therefrom.

Stephen V. Frye

5/5/99
Date

G1070USW

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,565,467

Date of Issue: July 31, 1996

Name of Patentee: Kenneth William BATCHELOR, et al.

Title of Invention: ANDROSTENONE DERIVATIVE

Assistant Commissioner for Patents
Washington, D.C. 20231

CONSENT OF ASSIGNEE TO CHANGE OF INVENTORSHIP IN PATENT (37 C.F.R. § 1.324)

Glaxo Wellcome Inc., owner by assignment of the above patent, in the assignment recorded in the PTO on March 16, 1995 at Reel 7406, Frame 0967, hereby consents to the amendment of the inventorship of this patent as requested in the accompanying papers.

Attached is a Certificate Under 37 CFR §3.73(b), establishing the right of the assignee to take action in this case.

Respectfully submitted,

GLAXO WELLCOME INC.

By: Robert H. Brink
Robert H. Brink
Reg. No. 36,094

Dated: May 17, 1999

Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, NC 27709
Telephone: (919)483-3323
Facsimile (919)483-7988

Attorney Docket : G1070USW

CERTIFICATE UNDER 37 C.F.R. §3.73(b)

Applicant: Kenneth William BATCHELOR; Stephen V. FRYE; George F. DORSEY, Jr.; and Robert A. MOOK, Jr.

Patent No.: 5,565,467 Issued: July 31, 1996

For: ANDROSTENONE DERIVATIVE

Glaxo Wellcome Inc. (Name of Assignee), a Corporation (Type of Assignee, e.g. corporation, partnership, university, etc.)

certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 7406, Frame 0967, or for which a copy thereof is attached.

B. [ ] A chain of title from the inventor(s), of the patent application identified above, to the current assignee as shown below:

1. From: _____ To: _____
   The document was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or which a copy thereof is attached.

2. From: _____ To: _____
   The document was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or which a copy thereof is attached.

3. From: _____ To: _____
   The document was recorded in the Patent and Trademark Office at Reel _____, Frame _____, or which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature: David J. Levy Date: MAY 17, 1999

Name: David J. Levy

Title: V.P. Intellectual Property Counsel, Assistant Secretary,

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE: 05/09/95
TO:

N05B

CHARLES E. DADSWELL
GLAXO INC.
LEGAL-PATENT GROUP
FIVE MOORE DRIVE
RTP, NC 27709

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR:
FRYE, STEPHEN V. DOC DATE: 03/16/95

ASSIGNOR:
MOOK, ROBERT A., JR. DOC DATE: 03/16/95

ASSIGNOR:
DORSEY, GEORGE F., JR. DOC DATE: 03/16/95

ASSIGNOR:
BATCHELOR, KENNETH W. DOC DATE: 03/16/95

RECORDATION DATE: 03/16/95 NUMBER OF PAGES 005 REEL/FRAME 7406/0967

DIGEST: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNEE:
GLAXO INC.
LEGAL-PATENT GROUP
5 MOORE DRIVE
RTP, NC 27709

SERIAL NUMBER 8-405120 FILING DATE 03/16/95
PATENT NUMBER ISSUE DATE 00/00/00

Dorothy E. Riley
EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

08/405120 D

US DEPARTMENT OF COMMERCE
Patent and Trademark Office

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10 MAR 16 1995
PAT. & TRADEMARK OFF

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Stephen V. Frye, Robert A. Mook, Jr., George F. Dorsey, Jr., Kenneth W. Batchelor

Additional name(s) of conveying party(ies) attached? No

3. Nature of conveyance: is

X Assignments Merger

Security Agreement Change of Name

Other

Execution Date: March 16, 1995

2. Name and address of receiving party(ies):

Name: GLAXO INC.

Internal Address: Legal-Patent Group

Street Address: 5 MOORE DRIVE

City: RTP State: NC Zip: 27709

Additional name(s) & address(es) attached? Yes No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: March 16, 1995

A. Patent Application No.(s)

B. Patent No.(s)

OIPE JC75
MAY 24 1995
PATENT & TRADEMARK OFFICE

Additional numbers attached? Yes X No

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REEL 7401 FRAME 0171

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Charles E. Dadswell

Internal Address: Glaxo Inc.
Legal-Patent Group

Street Address: Five Moore Drive

City: RTP State: NC Zip: 27709

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41):.....$ 40.00

Enclosed

X Authorized to be charged to deposit account.

Previously Submitted

8. Deposit account number: 07-1392

(Attach copy of this page if paying by deposit account)

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SC13130 04/03/95 08405120 07-1392 130 581 40.00CH

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Charles E. Dadswell
Name of Person Signing

Signature

03/16/95
Date

Total number of pages comprising cover sheet: 1

93770321

08/405120

G1070-2

ASSIGNMENT

I, Kenneth W. Batchelor, for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, Kenneth W. Batchelor, hereunto set my hand and seal this 11e day of March, 1995.

KWBatchelor
Kenneth W. Batchelor

State of North Carolina
County of Durham

Before me this 11e day of March 1995, personally appeared, Kenneth William Batchelor, who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Notary Public
My commission expires 11/15/97

G1070-2

ASSIGNMENT

I, Stephen Vernon Frye, for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, Stephen Vernon Frye, hereunto set my hand and seal this 16 day of March, 1995.

Stephen Vernon Frye

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, Stephen V. Frye, who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Notary Public
My commission expires 11/15/97

G1070-2

ASSIGNMENT

I, Robert A. Mook, Jr., for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, Robert A. Mook, Jr., hereunto set my hand and seal this 16 day of March, 1995.

R H A Mook Jr

Robert A. Mook, Jr.,

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, Robert A. Mook, Jr., who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Sharon Elizabeth Scott

Notary Public
My commission expires 11/15/97

RECEIVED

G1070-2

ASSIGNMENT

I, George F. Dorsey, Jr., for good and valuable consideration, receipt of which is hereby acknowledged, from GLAXO INC., a North Carolina corporation having its principal place of business in Research Triangle Park, NC, hereinafter called the Assignee, do hereby sell, assign and transfer unto the Assignee, its successors and assigns, the entire right, title and interest in, to and under an application for Letters Patent of the United States executed by us on the same date for:

ANDROSTENONE DERIVATIVE

and the inventions and any of them therein set forth and described, and any and all Letters patent of the United States and of countries foreign thereto which may be granted thereon or therefor including any continuation, division, renewal, substitute, reissue or extension thereof or any legal equivalent thereof.

For the above consideration, I agree promptly upon request of the Assignee, its successors or assigns, to execute and deliver without further compensation any power of attorney, continuation or reissue, or other papers which may be necessary or desirable fully to secure to the Assignee, its successors and assigns, the inventions and any of them described in said application and all patent rights therein, in the United States and in any country foreign thereto.

IN WITNESS WHERETO, I, George F. Dorsey, Jr., hereunto set my hand and seal this 16 day of March, 1995.

George F. Dorsey, Jr.

State of North Carolina
County of Durham

Before me this 16 day of March 1995, personally appeared, George F. Dorsey, Jr., who is to me personally known, and acknowledged the foregoing instrument of assignment to be his free act and deed.

Notary Public
My commission expires 11/15/97

RECORDED
PATENT & TRADEMARK OFFICE
MAR 16 95

EXHIBIT 7

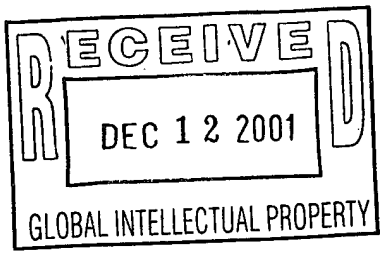
Maintenance Fee Statement for

U.S. Patent No. 5,565,467

Express Mail Label No.:
EL395889738US

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

IPSS



23347

elise

DAVID J LEVY, CORPORATE INTELLECTUAL PRO
GLAXOSMITHKLINE
FIVE MOORE DR.
PO BOX 13398
DURHAM NC 27709--339

G1070US2

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STA
1	5,565,467	183	830		08/405,120	10/15/96	03/16/95	04	NO	PAID

ITM NBR	ATTY DKT
1	

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231**

EXHIBITS 8A – 8B

Document Chronology/Due Diligence Logs for IND No. 47,838

Document Chronology/Due Diligence Logs for NDA 21-319

Express Mail Label No.:
EL395889738US

EXHIBIT 8A

Document Chronology/Due Diligence Logs for IND No. 47,838

Express Mail Label No.:
EL395889738US

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
22-Aug-1994	Food and Drug Administration Correspondence	Export	Authorization	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Export: Authorization			
26-Jan-1995	Food and Drug Administration Correspondence	Export	Authorization	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Export: Authorization			
03-Feb-1995	GlaxoSmithKline FAX/E-mail	Export		
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Export			
23-Feb-1995	Food and Drug Administration Correspondence	Export	Authorization	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Export: Authorization			
28-Feb-1995	GlaxoSmithKline Correspondence	General Correspondence		
	Pre-IND GI198745 (5-alpha reductase inhibitor) General Correspondence: Request for Comment			

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
24-Apr-1995	GlaxoSmithKline Correspondence	Initial Investigational New Drug Application	CMC Protocol(s) Included Study Reports	0000
		Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Initial Investigational New Drug Application: CMC, Protocol(s) Included, Study Reports Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0000			
28-Apr-1995	Food and Drug Administration Correspondence	Acknowledgement	IND # Assigned	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Acknowledgement: IND # Assigned			
09-May-1995	GlaxoSmithKline Correspondence	General Correspondence	Clinical Nonclinical	0001
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 001			

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-May-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Report of Selected Adverse Events Serial No.: 0002	General Correspondence	Report of Selected Adverse Events	0002
26-May-1995	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Record of Telecon	General Teleconference		
26-May-1995	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) FDA Comment	Comment/Information Request		
05-Jun-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Report of Selected Adverse Events Serial No.: 0003	General Correspondence	Report of Selected Adverse Events	0003
13-Jun-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 004	General Correspondence	Clinical	0004

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
13-Sep-1995	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add Investigator Add	0005
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0005			
26-Sep-1995	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0006
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0006			
10-Oct-1995	GlaxoSmithKline Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Other 1572 Change	0007
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 007			
13-Oct-1995	GlaxoSmithKline Telephone Conversation	General Teleconference	Nonclinical	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Record of Telecon			

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
16-Oct-1995	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Clinical	General Teleconference	Clinical	
18-Oct-1995	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: CMC	Comment/Information Request	CMC	
18-Oct-1995	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Minutes of Meeting: FDA Conference	Minutes of Meeting	FDA Conference	
25-Oct-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 008	General Correspondence		0008
03-Nov-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 0009	General Correspondence	Clinical	0009

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
08-Nov-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 010	Protocol Amendment: New Investigator	Investigator Add	0010
13-Nov-1995	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: CMC Serial No.: 0011	General Correspondence	CMC	0011
13-Dec-1995	GlaxoSmithKline Trip Report IND 47,838; GI198745 (5-alpha reductase inhibitor) Record of Visit to FDA	Topic		
29-Jan-1996	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls Information Amendment: Clinical Information Amendment: Nonclinical Protocol Amendment: New Protocol Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol	CMC Nonclinical Investigator Add Clinical	0012

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls Information Amendment: Clinical Information Amendment: Nonclinical Protocol Amendment: New Protocol Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol Serial No.: 0012			
29-Jan-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 0013	General Correspondence	Clinical	0013
08-Feb-1996	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) FDA Comment	Comment/Information Request	Clinical Nonclinical	
09-Feb-1996	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Clinical	General Teleconference	Clinical	

Regulatory Affairs

CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
12-Feb-1996	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical	Comment/Information Request	Clinical Efficacy	
22-Feb-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 014	Protocol Amendment: New Investigator	Investigator Add	0014
22-Feb-1996	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Electronic Submission	General Teleconference	Other	
29-Feb-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Nonclinical Serial No.: 015	Information Amendment: Nonclinical	Nonclinical Study Reports	0015
18-Mar-1996	GlaxoSmithKline Correspondence	General Correspondence	Clinical	0016

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 0016			
22-Mar-1996	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0017
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0017			
02-Apr-1996	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Nonclinical	Comment/Information Request	Nonclinical	
15-Apr-1996	GlaxoSmithKline Telephone Conversation	Response to FDA Request/Comment	Clinical Nonclinical	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Nonclinical			
19-Apr-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Nonclinical Serial No.: 0018	General Correspondence	Nonclinical	0018

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-Apr-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0019	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0019
24-Apr-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 020	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0020
24-Apr-1996	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical	Comment/Information Request	Clinical	
19-Jun-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 021	Protocol Amendment: New Investigator	Other 1572 Change	0021

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
24-Jun-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 5-Alpha Reductase Inhibitor Annual Report Serial No.: 022	Annual Report	CMC Foreign Marketing Developments	0022
29-Jul-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Nonclinical Serial No.: 0023	Response to FDA Request/Comment	Nonclinical	0023
14-Aug-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol Serial No.: 0024	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Protocol Amendment: Change in Protocol	Investigator Add Clinical	0024

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
29-Aug-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0025	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0025
11-Sep-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 026	Protocol Amendment: Change in Protocol	Clinical	0026
02-Oct-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 027	General Correspondence		0027
02-Oct-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence	General Correspondence	Other	
09-Oct-1996	Food and Drug Administration Telephone Conversation	Comment/Information Request		

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Request			
15-Oct-1996	GlaxoSmithKline Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add	0028
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 028			
15-Oct-1996	GlaxoSmithKline Telephone Conversation	General Teleconference	Meeting Request	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Meeting Request			
23-Oct-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details Serial No.: 0029	General Correspondence	Meeting Agenda or Details	0029
31-Oct-1996	Food and Drug Administration Correspondence	General Correspondence	Meeting Agenda or Details	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
04-Nov-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: CMC Serial No.: 0030	General Correspondence	CMC	0030
06-Nov-1996	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical	Comment/Information Request	Clinical	
15-Nov-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 0031	General Correspondence	Clinical	0031
18-Nov-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical, Meeting Agenda or Details Serial No.: 0032	General Correspondence	Clinical Meeting Agenda or Details	0032
26-Nov-1996	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Electronic Format	

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical, Electronic Format			
18-Dec-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details Serial No.: 0033	General Correspondence	Meeting Agenda or Details	0033
18-Dec-1996	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 0034	General Correspondence	Clinical	0034
28-Jan-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 035	Protocol Amendment: New Investigator	Other 1572 Change	0035
30-Jan-1997	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Record of Telecon	General Teleconference	CMC	

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Feb-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0036	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0036
04-Mar-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0037	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Other 1572 Change	0037
05-Mar-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 038	General Correspondence		0038
20-Mar-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 039	Protocol Amendment: New Investigator	Investigator Add	0039

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-May-1997	GlaxoSmithKline Correspondence	General Correspondence		0040
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 040			
02-Jun-1997	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Information Amendment: Chemistry Manufacturing and Controls Protocol Amendment: Change in Protocol	Investigator Add CMC Clinical	0041
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Information Amendment: Chemistry Manufacturing and Controls Serial No.: 0041			
03-Jun-1997	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0042
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0042			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
04-Jun-1997	GlaxoSmithKline Correspondence	General Correspondence		0043
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 043			
09-Jun-1997	GlaxoSmithKline Telephone Conversation	General Teleconference		
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Record of Telecon			
11-Jun-1997	GlaxoSmithKline Correspondence	Annual Report		0044
			CMC Foreign Marketing Developments	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Annual Report Serial No.: 044			
02-Jul-1997	GlaxoSmithKline Correspondence	Information Amendment: Clinical		
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Clinical Serial No.:045			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
22-Jul-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 046	Protocol Amendment: New Investigator	Investigator Add	0046
29-Jul-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 047	General Correspondence	CMC	0047
01-Aug-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence	General Correspondence	Other	
07-Aug-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 048	Protocol Amendment: New Investigator	Other 1572 Change	0048
13-Aug-1997	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	Investigator Add Transfer of Obligations to Contract	0049

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Research Organization	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0049			
15-Aug-1997	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls		0050
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 050			
19-Aug-1997	Food and Drug Administration Correspondence	Comment/Information Request	CMC	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: CMC			
20-Aug-1997	GlaxoSmithKline Correspondence	Minutes of Meeting	End of Phase II Meeting	0051
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Minutes of Meeting Serial No.: 051			
28-Aug-1997	Food and Drug Administration Correspondence	Comment/Information Request		
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
28-Aug-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 052	Protocol Amendment: New Investigator	Investigator Add	0052
08-Sep-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 053	General Correspondence	Clinical	0053
10-Sep-1997	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Minutes of Meeting: End of Phase II Meeting	Minutes of Meeting	End of Phase II Meeting	
11-Sep-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Other 1572 Change	0054

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0054			
11-Sep-1997	GlaxoSmithKline Telephone Conversation	General Teleconference		
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference			
19-Sep-1997	GlaxoSmithKline Telephone Conversation	General Teleconference		
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference			
22-Sep-1997	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0055
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0055			
25-Sep-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 56	Protocol Amendment: Change in Protocol	Clinical	0056

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
01-Oct-1997	GlaxoSmithKline Telephone Conversation	General Teleconference	Draft Protocol	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Draft Protocol			
02-Oct-1997	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0057
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0057			
09-Oct-1997	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls Information Amendment: Nonclinical	CMC Study Reports	0058
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 058 Information Amendment: Chemistry Manufacturing and Controls, CMC Information Amendment: Nonclinical, Study Reports			
10-Oct-1997	GlaxoSmithKline Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add Other 1572 Change	0059
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0059			

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
16-Oct-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 060 Annual Report: Changes to Investigator's Brochure Protocol Amendment: Change in Protocol	Annual Report Protocol Amendment: Change in Protocol	Changes to Investigator's Brochure Clinical Study Information Clinical	0060
21-Oct-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 061	General Correspondence	Statistical	0061
24-Oct-1997	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical	Comment/Information Request	Clinical	
27-Oct-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 062	Information Amendment: Chemistry Manufacturing and Controls		0062

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
31-Oct-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0063	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0063
03-Nov-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 064	Protocol Amendment: Change in Protocol	Clinical	0064
11-Nov-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0065	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0065
01-Dec-1997	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference	General Teleconference	Meeting Request	

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
02-Dec-1997	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Statistical	Response to FDA Request/Comment	Statistical	
03-Dec-1997	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Other	Comment/Information Request	CMC	
05-Dec-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comments Serial No.: 067	Response to FDA Request/Comment	CMC	0067
05-Dec-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0066	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0066
08-Dec-1997	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor)	Response to FDA Request/Comment	Clinical CMC	0068

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Correspondence Serial No.: 068			
15-Dec-1997	GlaxoSmithKline FAX/E-mail	Response to FDA Request/Comment General Memorandum	Statistical Meeting Agenda or Details	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Statistical			
15-Dec-1997	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Other	General Teleconference	Other	
08-Jan-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0069
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0069			
22-Jan-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 070	Protocol Amendment: Change in Protocol	Clinical	0070

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
29-Jan-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0071	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0071
04-Feb-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Statistical Serial No.: 072	General Correspondence	Statistical	0072
11-Feb-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 073	General Correspondence	Clinical Draft Protocol	0073
18-Feb-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Clinical Request for waivers for non-US Studies Serial No.: 075	Information Amendment: Clinical	Other	0075

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
18-Feb-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 074	General Correspondence	Statistical	0074
26-Feb-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0076	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add Other 1572 Change	0076
06-Mar-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 077	Information Amendment: Chemistry Manufacturing and Controls	CMC	0077
27-Mar-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0078	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0078

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
02-Apr-1998	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical	Comment/Information Request	Clinical	
03-Apr-1998	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request	Comment/Information Request	Statistical	
09-Apr-1998	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: CMC	General Teleconference	CMC	
17-Apr-1998	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical	Comment/Information Request	Clinical	
23-Apr-1998	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor)	General Teleconference	CMC	

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Teleconference: CMC			
27-Apr-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0079	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0079
28-Apr-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 080	Protocol Amendment: Change in Protocol	Clinical	0080
30-Apr-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 081	Protocol Amendment: Change in Protocol	Clinical	0081
11-May-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 082	General Correspondence	Clinical	0082

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
12-May-1998	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Protocol	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical, Protocol			
28-May-1998	Food and Drug Administration Correspondence	Comment/Information Request	Clinical Statistical	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical, Statistical			
29-May-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0083
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0083			
29-May-1998	GlaxoSmithKline Telephone Conversation	Response to FDA Request/Comment	Clinical Protocol	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Clinical			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Jun-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Annual Report Serial No.: 084	Annual Report	Adverse Event Summary Clinical Study Information CMC Outstanding Regulatory Business	0084
19-Jun-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 085	General Correspondence	Clinical	0085
22-Jun-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Serial No.: 086	Protocol Amendment: New Protocol		0086
23-Jun-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor)	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0087

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Investigator Serial No.: 0087			
01-Jul-1998	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0088
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 088			
09-Jul-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add	0089
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0089			
31-Jul-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0090	Protocol Amendment: Change in Protocol	Clinical	0090
03-Aug-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0091

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0091			
10-Aug-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 092	Protocol Amendment: Change in Protocol	Clinical	0092
31-Aug-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0093
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0093			
14-Sep-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0094
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0094			
06-Oct-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator		0095

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Investigator Add	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0095			
13-Oct-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0096
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0096			
28-Oct-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0097
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0097			
06-Nov-1998	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0098
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0098			

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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Nov-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 099	Protocol Amendment: Change in Protocol	Clinical	0099
18-Nov-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0100	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0100
17-Dec-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0101	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0101
22-Dec-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0102	Protocol Amendment: New Investigator	Other 1572 Change	0102
23-Dec-1998	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor)	Protocol Amendment: New Investigator	Investigator Add	0103

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Investigator Serial No.: 103			
13-Jan-1999	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0104
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 104			
15-Jan-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0105
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0105			
02-Feb-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0106
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0106			
18-Feb-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0107
	IND 47,838; GI198745 (5-alpha reductase inhibitor)			

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0107			
03-Mar-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0108
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0108			
04-Mar-1999	GlaxoSmithKline Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0109
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 109			
08-Mar-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0110
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 110			
12-Mar-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor)	Protocol Amendment: Change in Protocol	Clinical	0111

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: Change in Protocol Serial No.: 111			
19-Mar-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0112
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0112			
02-Apr-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Amendment: Other, Change in Medical Monitor Serial No.: 113	Amendment: Other	Change in Medical Monitor	0113
06-Apr-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 114	Protocol Amendment: New Investigator	Other 1572 Change	0114
27-Apr-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0115	Protocol Amendment: New Investigator	Other 1572 Change	0115

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
29-Apr-1999	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: CMC	General Teleconference	CMC	
19-May-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Statistical Serial No.: 0116	General Correspondence	Statistical	0116
21-May-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0117	Protocol Amendment: New Investigator	Other 1572 Change	0117
09-Jun-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0119	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add	0119

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Jun-1999	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0118 0018
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0118			
10-Jun-1999	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Status Update	General Teleconference	Status Update	
22-Jun-1999	GlaxoSmithKline Correspondence	Annual Report	Adverse Event Summary Clinical Study Information CMC Investigational Plan Outstanding Regulatory Business	0120
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Annual Report Serial No.: 0120			
24-Jun-1999	GlaxoSmithKline Correspondence	General Correspondence	CMC	0121
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Injection, 0.0111 mg GI198745X per mL General Correspondence: CMC -Phase I IV Solution			

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0121			
24-Jun-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 Soft Gelatin Capsules, 0.5 mg General Correspondence: CMC - Specification and Test Methods Serial No.: 0122	General Correspondence	CMC	0122
02-Jul-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0123	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0123
06-Jul-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0124	Protocol Amendment: New Investigator	Other 1572 Change	0124
15-Jul-1999	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Other	Comment/Information Request	Other	

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
20-Jul-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0125	Protocol Amendment: New Investigator	Other 1572 Change	0125
21-Jul-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0126	Protocol Amendment: Change in Protocol	Clinical	0126
22-Jul-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 0127	General Correspondence	Clinical	0127
30-Jul-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0128	Protocol Amendment: New Investigator	Other 1572 Change	0128
17-Aug-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0129	Protocol Amendment: New Investigator	Other 1572 Change	0129

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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
01-Sep-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0130	Information Amendment: Chemistry Manufacturing and Controls	CMC	0130
01-Sep-1999	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Clinical, Safety	General Teleconference	Clinical Safety	
09-Sep-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details Serial No.: 0131	General Correspondence	Meeting Agenda or Details	0131
	IND 53,551; GI262570X General Correspondence: Meeting Agenda or Details Serial No.: 0072			
10-Sep-1999	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Status Update	General Teleconference	Status Update	

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
24-Sep-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0132 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0021 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0132
26-Oct-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Improper Conduct by an Investigator Serial No.: 0133	Improper Conduct by an Investigator		0133
28-Oct-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Statistical Serial No.: 0134	General Correspondence	Statistical	0134
28-Oct-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Minutes of Meeting Serial No.: 0135	Minutes of Meeting	FDA Conference	0135
28-Oct-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor)	15-Day ADR Report	Initial	0136

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CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0136 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0023 10-Day ADR Report: Initial			
01-Nov-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 0137	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0137
02-Nov-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Clinical, Statistical Serial No.: 0138	Information Amendment: Clinical	Statistical	0138
10-Nov-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence Serial No.: 0139	General Correspondence	Clinical	0139
22-Nov-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0140	Protocol Amendment: Change in Protocol	Clinical	0140

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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
03-Dec-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0141	Protocol Amendment: Change in Protocol	Clinical	0141
08-Dec-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0142	Protocol Amendment: New Investigator	Investigator Add	0142
10-Dec-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0143 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0024 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0143
15-Dec-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0144	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0144

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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
22-Dec-1999	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Statistical Serial No.: 0145	General Correspondence	Statistical	0145
28-Dec-1999	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Statistical	Comment/Information Request	Statistical	
05-Jan-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0146 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0025 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0146
05-Jan-2000	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Other	General Teleconference	Other	
06-Jan-2000	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Other	General Teleconference	Other	

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Jan-2000	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Other	Comment/Information Request	Other	
11-Jan-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0147	Protocol Amendment: New Investigator	Other 1572 Change Investigator Add	0147
11-Jan-2000	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Safety	Response to FDA Request/Comment	Safety	
17-Jan-2000	GlaxoSmithKline FAX/E-mail IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Other	Response to FDA Request/Comment	Other	
19-Jan-2000	GlaxoSmithKline Correspondence	15-Day ADR Report	Follow-up	0148

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0148 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0027 10-Day ADR Report: Follow-up			
02-Feb-2000	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0150
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0150			
02-Feb-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0149 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0028 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0149
24-Feb-2000	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0151
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0151			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
14-Mar-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Amendment: Other, Letter of Authorization Serial No.: 0153	Amendment: Other	Letter of Authorization	0153
14-Mar-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0152	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add	0152
30-Mar-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0154 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0030 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0154
14-Apr-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0155	Protocol Amendment: New Investigator	Investigator Add	0155
21-Apr-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Other	

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Other			
03-May-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0156 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0031 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0156
05-May-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0157 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0032 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0157
19-May-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0158	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0158
23-May-2000	GlaxoSmithKline FAX/E-mail delete me!	General Memorandum	Safety	

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-May-2000	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) 7-Day Safety Report	7-Day Safety Report	Safety	
24-May-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0159 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0033 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0159
09-Jun-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0160 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0034 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0160
15-Jun-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0161	Protocol Amendment: New Investigator	Other 1572 Change	0161

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-Jun-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0162 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0035 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0162
27-Jun-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Annual Report Serial No.: 0163	Annual Report	Clinical Study Information Investigational Plan	0163
13-Jul-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0164	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0164
13-Jul-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0165 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0036 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0165

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
17-Jul-2000	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) 7-Day Safety Report	7-Day Safety Report	Safety	
18-Jul-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0166 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0037 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0166
08-Aug-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0167	Protocol Amendment: Change in Protocol	Clinical	0167
16-Aug-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0168	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0168

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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
17-Aug-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0169 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0038 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0169
21-Aug-2000	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) 7-Day Safety Report	7-Day Safety Report	Safety	
22-Aug-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0170 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0039 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0170
24-Aug-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0171 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0040 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0171
24-Aug-2000	GlaxoSmithKline Correspondence	Information Amendment: Clinical	Other	0172

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
		General Correspondence	Draft Protocol	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Clinical, Other Serial No.: 0172			
28-Aug-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: CMC Serial No.: 0173	General Correspondence	CMC	0173
19-Sep-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Clinical Serial No.: 0174	General Correspondence	Clinical	0174
20-Sep-2000	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0175
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0175			
22-Sep-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Request Serial No.: 0176	General Correspondence	Meeting Request	0176

Regulatory Affairs
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Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
26-Sep-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Protocol Serial No.: 0177	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0177
26-Sep-2000	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Status Update	General Teleconference	Status Update	
27-Sep-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: CMC Meeting Request Serial No.: 0178	General Correspondence	CMC	0178
03-Oct-2000	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: Meeting Request	General Teleconference	Meeting Request	
06-Oct-2000	Food and Drug Administration Correspondence	General Correspondence	Meeting Agenda or Details	

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details			
13-Oct-2000	GlaxoSmithKline Telephone Conversation	General Teleconference	CMC Meeting Agenda or Details	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: CMC, Meeting Agenda or Details			
17-Oct-2000	Food and Drug Administration Correspondence	Comment/Information Request	Clinical Protocol	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request			
17-Oct-2000	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request			
19-Oct-2000	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0179

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0179			
23-Oct-2000	Food and Drug Administration FAX/E-mail	General Memorandum Comment/Information Request	Meeting Agenda or Details CMC	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Memorandum: Meeting Agenda or Details Comment/Information Request: CMC			
27-Oct-2000	GlaxoSmithKline Correspondence	General Correspondence	Clinical Meeting Agenda or Details Nonclinical Protocol	0180
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details Pre-NDA Meeting Information Package Serial No.: 0180			
30-Oct-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0181	Protocol Amendment: Change in Protocol	Clinical	0181

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
02-Nov-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0182	Protocol Amendment: Change in Protocol	Clinical	0182
06-Nov-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0183 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0041 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0183
07-Nov-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Clinical, Statistical Serial No.: 0184	Information Amendment: Clinical	Statistical	0184
09-Nov-2000	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: CMC	General Teleconference	CMC Meeting Agenda or Details	

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Nov-2000	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details	General Correspondence	Meeting Agenda or Details	
17-Nov-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0185	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0185
17-Nov-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: CMC Serial No.: 0186	Response to FDA Request/Comment	CMC	0186
27-Nov-2000	Food and Drug Administration Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Clinical Comment on Pre-NDA Meeting Package	Comment/Information Request	Clinical	
30-Nov-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0187 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia	15-Day ADR Report	Follow-up	0187

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0042 10-Day ADR Report: Follow-up			
01-Dec-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Serial No.: 0188	Protocol Amendment: Change in Protocol	Clinical	0188
05-Dec-2000	GlaxoSmithKline Trip Report IND 47,838; GI198745 (5-alpha reductase inhibitor) Type: Pre-NDA Meeting	Type	Pre-NDA Meeting	
05-Dec-2000	Food and Drug Administration Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details	General Correspondence	Meeting Agenda or Details	
06-Dec-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Meeting Agenda or Details Serial No.: 0189	General Correspondence	Meeting Agenda or Details	0189
08-Dec-2000	GlaxoSmithKline Correspondence	General Correspondence	Nonclinical	0190

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) General Correspondence: Nonclinical Serial No.: 0190			
14-Dec-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0191	Protocol Amendment: New Investigator	Other 1572 Change	0191
15-Dec-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: Clinical, Draft Protocol Serial No.: 0192	Response to FDA Request/Comment	Clinical Draft Protocol	0192
18-Dec-2000	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0193 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0043 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0193
02-Jan-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0194 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia	15-Day ADR Report	Initial	0194

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0044 10-Day ADR Report: Initial			
03-Jan-2001	Food and Drug Administration Correspondence	Comment/Information Request	Statistical	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Comment/Information Request: Statistical			
08-Jan-2001	GlaxoSmithKline Correspondence	15-Day ADR Report	Follow-up	0195
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0195 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0045 10-Day ADR Report: Follow-up			
09-Jan-2001	GlaxoSmithKline Telephone Conversation	7-Day Safety Report	Safety	
	IND 47,838; GI198745 (5-alpha reductase inhibitor) 7-Day Safety Report			
10-Jan-2001	GlaxoSmithKline Correspondence	15-Day ADR Report	Initial	0196
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0196 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0046 10-Day ADR Report: Initial			

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
11-Jan-2001	GlaxoSmithKline Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0197
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0197			
12-Jan-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0198 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0048 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0198
02-Feb-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Response to FDA Request/Comment: CMC Teleconference Held on November 9, 2000 Serial No.: 0199	Response to FDA Request/Comment	CMC	0199
08-Feb-2001	GlaxoSmithKline Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add Other 1572 Change	0200
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator			

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0200			
08-Feb-2001	GlaxoSmithKline Telephone Conversation IND 47,838; GI198745 (5-alpha reductase inhibitor) General Teleconference: CMC	General Teleconference	CMC	
19-Feb-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0201 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0049 10-Day ADR Report: Initial	15-Day ADR Report	Initial	0201
05-Mar-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0202 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0050 10-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0202
09-Mar-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0203	Protocol Amendment: New Investigator	Other 1572 Change	0203

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
30-Mar-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Information Amendment: Clinical Serial No.: 0204	Information Amendment: Clinical	Other	0204
09-Apr-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0205	Protocol Amendment: New Investigator	Other 1572 Change	0205
08-May-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0206	Protocol Amendment: New Investigator	Other 1572 Change	0206
07-Jun-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0207	Protocol Amendment: New Investigator	Other 1572 Change	0207
21-Jun-2001	GlaxoSmithKline Correspondence	Annual Report	Adverse Event Summary Changes to Investigator's Brochure Clinical Study Information CMC	0208

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 47,838; GI198745 (5-alpha reductase inhibitor) Annual Report Serial No.: 0208			
18-Jul-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0209 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0051 15-Day ADR Report: Initial	15-Day ADR Report	Initial	0209
25-Jul-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0210	Protocol Amendment: New Investigator	Other 1572 Change	0210
27-Jul-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0211 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0052 15-Day ADR Report: Follow-up	15-Day ADR Report	Follow-up	0211
06-Aug-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0212	15-Day ADR Report	Follow-up	0212

Regulatory Affairs
CARDS
Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0053 15-Day ADR Report: Follow-up			
31-Aug-2001	GlaxoSmithKline Correspondence IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0054 IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0213 General Correspondence: Clinical	General Correspondence	Clinical	0213
05-Sep-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Serial No.: 0214 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0055 15-Day ADR Report: Initial	15-Day ADR Report	Initial	0214
06-Sep-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0215	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0215
20-Sep-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor)	15-Day ADR Report	Follow-up	0216

Regulatory Affairs
CARDS

Chronology

Application: IND 47838; GI198745 (5-alpha reductase inhibitor)

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 0216 IND 54,319; GI198745 (5-alpha reductase inhibitor) Alopecia Serial No.: 0056 15-Day ADR Report: Follow-up			
08-Oct-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0217	Protocol Amendment: New Investigator	Other 1572 Change	0217
07-Nov-2001	GlaxoSmithKline Correspondence IND 47,838; GI198745 (5-alpha reductase inhibitor) Protocol Amendment: New Investigator Serial No.: 0218	Protocol Amendment: New Investigator	Other 1572 Change	0218
30-Nov-2001	GlaxoSmithKline Correspondence NAS; Not Product Specific General Correspondence: Other	General Correspondence		0219

EXHIBIT 8B

Document Chronology/Due Diligence Logs for NDA 21-319

Express Mail Label No.:
EL395889738US

Regulatory Affairs

CARDS
Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
22-Sep-2000	Food and Drug Administration FAX/E-mail	General Memorandum	Status Update	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Memorandum: User Fee ID #			
06-Oct-2000	Food and Drug Administration Correspondence	General Correspondence	Meeting Agenda or Details	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: Meeting Agenda or Details			
19-Dec-2000	GlaxoSmithKline Correspondence	User Fee	Establishment With Clinical Data	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules User Fee ID Number 4030: Establishment With Clinical Data			
19-Dec-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: Status Update			
19-Dec-2000	GlaxoSmithKline Telephone Conversation	General Teleconference	Request Status Update	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: Request Status Update			

Regulatory Affairs

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Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
21-Dec-2000	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC Field Copy	General Correspondence	CMC Field Copy	
21-Dec-2000	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Original Submission	Original Submission User Fee General Correspondence	Establishment Clinical CMC Field Copy DMF Nonclinical Patent Information	
02-Jan-2001	Food and Drug Administration Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Desk Copies	Comment/Information Request	Other	

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
03-Jan-2001	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Desk Copies	Response to FDA Request/Comment	Other	
26-Jan-2001	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment	Response to FDA Request/Comment	Clinical Statistical	
01-Feb-2001	GlaxoSmithKline Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC	Response to FDA Request/Comment	CMC	
01-Feb-2001	GlaxoSmithKline Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC	Response to FDA Request/Comment	CMC	

Regulatory Affairs

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Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
02-Feb-2001	GlaxoSmithKline Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC	Response to FDA Request/Comment	CMC	
06-Feb-2001	Food and Drug Administration Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request	Comment/Information Request	Clinical Statistical	
08-Feb-2001	Food and Drug Administration Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request	Comment/Information Request	CMC Electronic Format Nonclinical	
08-Feb-2001	GlaxoSmithKline Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules	General Teleconference	Clinical CMC Meeting Agenda or Details	

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Teleconference: Meeting Agenda or Details			
13-Feb-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request for Information on Clinical Investigators			
21-Feb-2001	GlaxoSmithKline Correspondence	General Correspondence	Meeting Agenda or Details Other	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: Meeting Agenda or Details, Other			
01-Mar-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Clinical CMC Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment			
20-Apr-2001	GlaxoSmithKline Correspondence	120-Day Safety Update	Safety	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules			

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	120-Day Safety Update: Safety			
07-May-2001	GlaxoSmithKline FAX/E-mail	General Memorandum	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Memorandum: CMC			
08-May-2001	GlaxoSmithKline Telephone Conversation	Response to FDA Request/Comment	Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Nonclinical			
08-May-2001	Food and Drug Administration Correspondence	Minutes of Meeting	FDA Conference	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of Meeting			
09-May-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC			
15-May-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC	

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC			
12-Jun-2001	GlaxoSmithKline Telephone Conversation	General Teleconference	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: CMC			
12-Jun-2001	Food and Drug Administration Correspondence	Minutes of Meeting Comment/Information Request	FDA Conference CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of Meeting: FDA Conference			
14-Jun-2001	GlaxoSmithKline Telephone Conversation	General Teleconference	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: CMC			
15-Jun-2001	GlaxoSmithKline Correspondence	Amendment to Pending Application	Clinical Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules			

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Amendment to Pending Application: Clinical, Nonclinical			
27-Jun-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC-Site Change for the Blister Pack Foil Lidding			
27-Jun-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC Meeting Minutes for June 14, 2001			
27-Jun-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC Field Copy	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC Field Copy			
27-Jun-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC - 36-Month Stability Update			
27-Jun-2001	GlaxoSmithKline Correspondence	User Fee	Response to Reconciliation Request	

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	FDA Invoice 975586 User Fee: Response to Reconciliation Request			
	NDA 19-958; CUTIVATE® (fluticasone propionate cream) Cream, 0.05% NDA 21-254; ADVAIR™ HFA (fluticasone propionate/salmeterol) Inhalation Aerosol 44mcg/21mcg, 110mcg/21mcg, 220mcg/21mcg NDA 21-319; Dutasteride Soft-Gelatin Capsules			
27-Jun-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC Field Copy	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC Field Copy			
02-Jul-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Other	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Other, Financial Disclosure			
02-Jul-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Nonclinical			
09-Jul-2001	GlaxoSmithKline Correspondence	Amendment to Pending Application	Labeling	

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Amendment to Pending Application: Tradename; Labeling			
13-Jul-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling			
16-Jul-2001	GlaxoSmithKline Telephone Conversation	General Teleconference	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: CMC			
16-Jul-2001	GlaxoSmithKline Correspondence	Minutes of Meeting	FDA Conference	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of Meeting			
20-Jul-2001	GlaxoSmithKline Correspondence	Amendment to Pending Application	Clinical Labeling Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Amendment to Pending Application: Labeling, Nonclinical, Human Pharmacokinetics			

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Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
20-Jul-2001	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Statistical	Response to FDA Request/Comment	Statistical	
26-Jul-2001	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Nonclinical	Response to FDA Request/Comment	Nonclinical	
30-Jul-2001	GlaxoSmithKline Telephone Conversation NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment	Response to FDA Request/Comment	Nonclinical	
30-Jul-2001	Food and Drug Administration Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of Meeting	Minutes of Meeting	FDA Conference	
02-Aug-2001	Food and Drug Administration FAX/E-mail	Comment/Information Request	Nonclinical	

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Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Nonclinical			
07-Aug-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Nonclinical			
14-Aug-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Statistical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Statistical			
20-Aug-2001	Food and Drug Administration Correspondence	Comment/Information Request	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: CMC			
23-Aug-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Clinical Efficacy	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment			

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Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
04-Sep-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Nonclinical			
06-Sep-2001	GlaxoSmithKline Telephone Conversation	Response to FDA Request/Comment	Statistical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Statistical			
07-Sep-2001	GlaxoSmithKline Correspondence	General Correspondence	Clinical Statistical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: Clinical, Statistical			
07-Sep-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC - August 27, 2001			
10-Sep-2001	Food and Drug Administration Correspondence	User Fee Invoice	Product	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules			

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Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	User Fee Invoice			
13-Sep-2001	GlaxoSmithKline Telephone Conversation	Response to FDA Request/Comment	Clinical Statistical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Clinical, Statistical			
19-Sep-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Clinical Statistical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Clinical, Statistical			
25-Sep-2001	GlaxoSmithKline Telephone Conversation	General Teleconference	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: CMC			
26-Sep-2001	GlaxoSmithKline Telephone Conversation	General Teleconference	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: CMC			

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Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
27-Sep-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC			
01-Oct-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC			
04-Oct-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC			
04-Oct-2001	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Clinical			
09-Oct-2001	GlaxoSmithKline Correspondence	Amendment to Pending Application	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Amendment to Pending Application: CMC			

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Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Oct-2001	Food and Drug Administration Telephone Conversation	General Teleconference	Meeting Agenda or Details Meeting Request	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: Meeting Request			
09-Oct-2001	Food and Drug Administration Correspondence	Minutes of Meeting Comment/Information Request	FDA Conference CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of September 25 CMC Meeting			
10-Oct-2001	Food and Drug Administration Correspondence	Minutes of Meeting	FDA Conference	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of Meeting: FDA Conference			
11-Oct-2001	GlaxoSmithKline Correspondence	Amendment to Pending Application	CMC	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Amendment to Pending Application: CMC			

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Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
11-Oct-2001	GlaxoSmithKline Correspondence	General Correspondence	CMC Field Copy	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: CMC Field Copy			
11-Oct-2001	GlaxoSmithKline Telephone Conversation	General Teleconference	Clinical Nonclinical Safety	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Teleconference: Clinical, Nonclinical, Safety			
15-Oct-2001	GlaxoSmithKline Correspondence	General Correspondence	Labeling Other	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules General Correspondence: Other, Trade Name			
15-Oct-2001	GlaxoSmithKline Telephone Conversation	Response to FDA Request/Comment	Advisory Committee Meeting	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment Clinical Pharmacology and Biopharmaceutics Review Letter			

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Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
17-Oct-2001	Food and Drug Administration Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Minutes of Meeting: FDA Conference	Minutes of Meeting	FDA Conference	
18-Oct-2001	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules NDA 20-241; LAMICTAL® (lamotrigine) Tablets General Correspondence: Request for a User Fee Refund Check	General Correspondence	Other	
24-Oct-2001	GlaxoSmithKline Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: CMC	Response to FDA Request/Comment	CMC	
24-Oct-2001	Food and Drug Administration Correspondence NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Labeling	Comment/Information Request	Labeling	
31-Oct-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	BA/BE Clinical	

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Chronology

Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment			
02-Nov-2001	GlaxoSmithKline FAX/E-mail	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling			
05-Nov-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling			
07-Nov-2001	Food and Drug Administration Correspondence	User Fee Invoice Comment/Information Request		
	NDA 21-319; Dutasteride Soft-Gelatin Capsules NDA 20-241; LAMICTAL® (lamotrigine) Tablet Re: GlaxoSmithKline, Request for Refund of Application Fees User fee ID #4203 and #4204			

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Application: NDA 21319; Dutasteride Soft-Gelatin Capsules

Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
08-Nov-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling			
08-Nov-2001	Food and Drug Administration FAX/E-mail	Comment/Information Request	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Labeling			
08-Nov-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling, Packaging			
13-Nov-2001	Food and Drug Administration FAX/E-mail	Comment/Information Request	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Labeling			
15-Nov-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Nonclinical	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Nonclinical; Phase 4 Comittment			

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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
16-Nov-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling			
16-Nov-2001	Food and Drug Administration FAX/E-mail	Comment/Information Request	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Comment/Information Request: Labeling			
19-Nov-2001	GlaxoSmithKline Correspondence	Response to FDA Request/Comment	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Response to FDA Request/Comment: Labeling			
20-Nov-2001	Food and Drug Administration Correspondence	Approval Letter	Labeling	
	NDA 21-319; Dutasteride Soft-Gelatin Capsules Approval Letter			
30-Nov-2001	GlaxoSmithKline Correspondence	General Correspondence		
	General Correspondence: Other Notification of Corporation Name Change - Reproductive and Urologic			

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CARDS
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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

EXHIBIT 9

Patent Term Extension Calculations for

Patent Term Extension of

U.S. Patent No. 5,565,467

Express Mail Label No.:
EL395889738US

Patent Term Extension Calculation for U.S. Patent No. 5,565,467

Patent Issue Date: **15 Oct 1996**

Period of Testing Phase -- IND 47,838

24 April 1995 through

20 December 2000 is:

24 Apr 95 – 23 Apr 96 =	366
24 Apr 96 – 23 Apr 97 =	365
24 Apr 97 – 23 Apr 98 =	365
24 Apr 98 – 23 Apr 99 =	365
24 Apr 99 – 24 Apr 00 =	366
24 Apr 00 – 23 May 00 =	29
24 May 00 – 23 Jun 00 =	31
24 Jun 00 – 23 Jul 00 =	30
24 Jul 00 – 23 Aug 00 =	31
24 Aug 00 – 23 Sep 00 =	31
24 Sep 00 – 23 Oct 00 =	30
24 Oct 00 – 23 Nov 00 =	31
24 Nov 00 – 20 Dec 00 =	27
	2067 days

Period of IND post-patent issuance

24 April 1995 through

15 October 1996 is:

24 Apr 95 – 23 Apr 96 =	365 days
24 Apr 96 – 23 May 96 =	29
24 May 96 – 23 Jun 96 =	31
24 Jun 96 – 23 Jul 96 =	30
24 Jul 96 – 23 Aug 96 =	31
24 Aug 96 – 23 Sep 96 =	31
24 Sep 96 – 15 Oct 96 =	22
	539 days

Applicable Period of Testing Phase

2067 days – 539 days = 1528 days

Testing Phase

IND Phase / 2 = 1528 / 2 = **764 days**

Period of Approval Phase – NDA 21-319

NDA Submission Date:	21 Dec 2000
NDA Approval Date:	20 Nov 2001

Period of Approval Phase:

21 Dec 00 – 31 Dec 00 =	10
1 Jan 01 – 31 Jan 01 =	31
1 Feb 01 – 29 Feb 01 =	28
1 Mar 01 – 31 Mar 01 =	31
1 Apr 01 – 30 Apr 01 =	30
1 May 01 – 31 May 01 =	31
1 Jun 01 – 30 Jun 01 =	30
1 Jul 01 – 31 Jul 01 =	31
1 Aug 01 – 31 Aug 01 =	31
1 Sep 01 – 30 Sep 01 =	30
1 Oct 01 – 31 Oct 01 =	31
1 Nov 01 – 20 Nov 01 =	20
	334 days

IND phase/2 + NDA phase = 764+334 = 1098

Total Patent Term Extension: **1098 days**

Expiration + 1098-Day Patent Term Extension: **18 Oct 2016**

<u>14 Year Cap from NDA Approval Date:</u>

NDA Approval Date + 14 yrs=

20 Nov 01 + 14 yrs = 20 Nov 2015

14 year Patent Term Cap applies.

Patent Term Extension subject to 14 Year Cap: **769 days**

Expiry with Extension: **20 Nov 2015**